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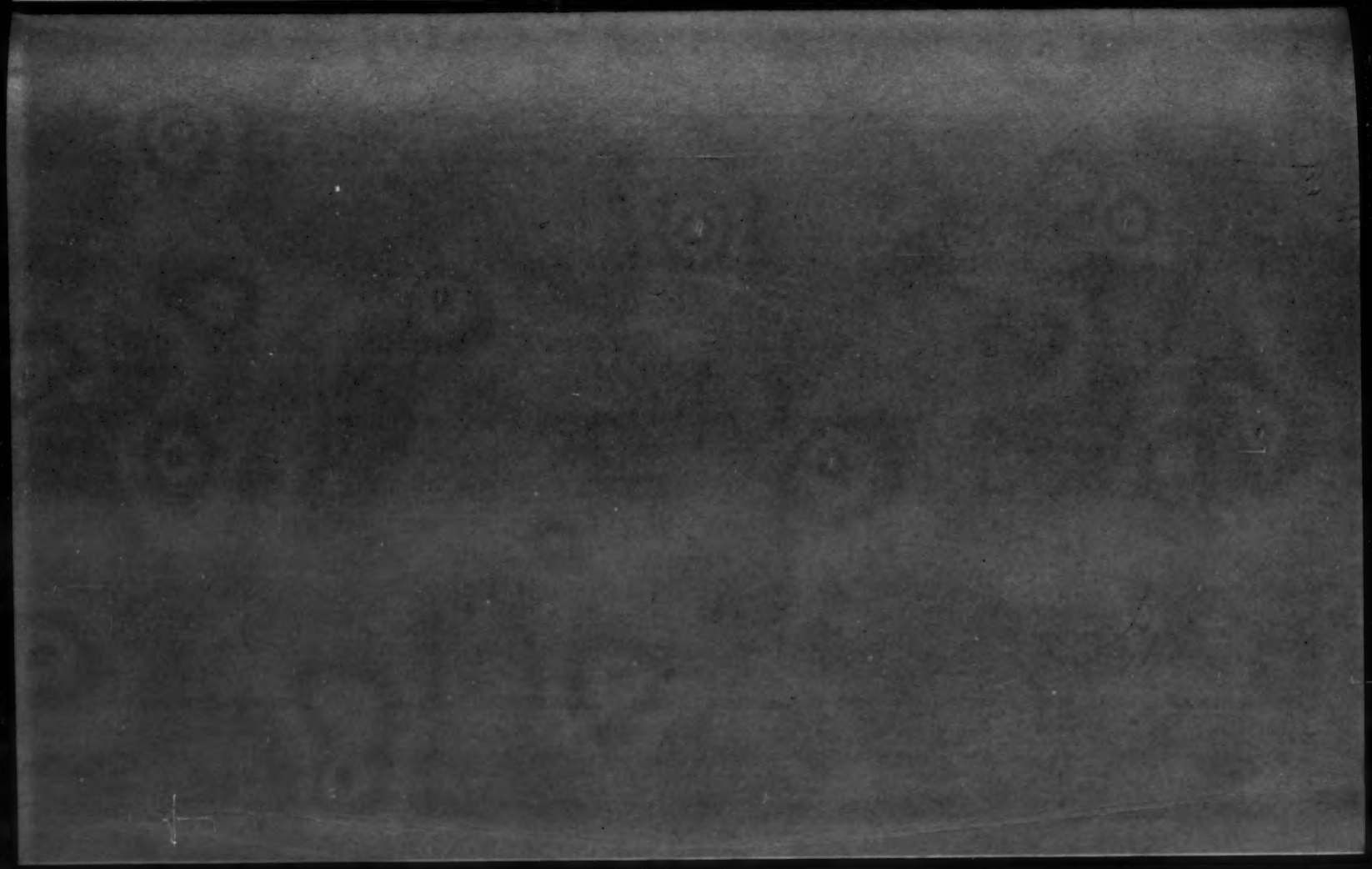

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THE NEW YORK ACADEMY
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PUERPERAL INFECTION

*A consideration of the relationship of pathological changes and bacteriological findings to prevention and treatment**

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PUERPERAL infection may be defined as an invasion of the genital tract by pathogenic organisms during pregnancy, labor or the puerperium. Descriptions of this disease have been found in the earliest medical records and it has undoubtedly existed since the origin of the human race. Limitation of time prevents a review of the long history of the struggle of the physician to explain and conquer this most frequent complication of pregnancy and compels me to proceed at once to a discussion limited to certain aspects of this condition.

Before considering the disease itself it would be well to review briefly from the point of view of infection, the conditions which exist in the genital tract during pregnancy, labor and the puerperium under normal circumstances. The two chief points to be emphasized are the presence of organisms in or about the genital tract and the changes brought about by labor and delivery which favor the onset of infection.

* Read October 22, 1940 before the Graduate Fortnight of The New York Academy of Medicine.

Organisms have been shown to be present about and in the lower genital tract below the level of the cervical external os in all normal pregnant women. Staphylococci may be recovered from the skin of the vulva and perineum. B. coli may be found on the perineal skin and about the anus. The latter organism is not commonly found in the vagina unless marked relaxation of the perineum or urinary infection exists.[1] Present in the vagina itself may be found a variety of organisms, among which may be mentioned Döderlein's bacillus, indifferent aerobic streptococci, Streptococcus viridans, diphtheroids, anaerobic streptococci and other organisms. The anaerobic streptococcus is found very frequently[2, 3] and it has been stated by Hare[4] that the vagina is the only situation in nature that this organism is found with any frequency. All investigators of the normal vaginal flora in pregnancy agree that hemolytic streptococci are rarely found, the incidence being usually stated at between 1 per cent[3] and 3 per cent.[5] It is also generally agreed that when these organisms are found to be present, evidence of pathogenicity, as shown by puerperal fever, rarely occurs. It has been shown that these hemolytic streptococci almost never belong to Group A, the cause of most human infection by this organism.[6] Furthermore, it has been found that when virulent hemolytic streptococci are placed in the vaginas of experimental animals, they disappear with great rapidity.[7]

The genital tract above the external os must be considered as uncontaminated by bacteria. It is probable that the defensive activity of the tissue and the cervical mucous plug prevent their intrusion above this point. This statement is almost certainly true in the primipara but deep old cervical lacerations may permit some contamination of the canal in multiparae. The one exception that comes to mind is the individual who has a latent gonorrheal infection of the cervix during pregnancy. Certainly one must consider the cavity of the uterus and its contained ovum to be sterile above the level of the internal os during pregnancy. In the normal pregnant woman this state of affairs is disturbed by the onset of labor and this is particularly true if premature rupture of the amniotic sac takes place. Impelled by the uterine contractions, the presenting part, with or without the bag of forewaters, is forced down into the dilating cervix. The latter structure becomes separated from the adjacent membranes and the mucous plug is expelled. The presenting part with or without its covering of membranes becomes contaminated with vaginal organisms. During the period of uterine relaxation the presenting part

ascends carrying with it those organisms which contaminate the lower uterine segment. If the membranes are ruptured, the residual amniotic fluid likewise becomes infected. Occasionally the amniotic sac becomes infected without any evidence of preceding rupture, but ordinarily it is resistant to the penetration of organisms.[8] This quality is of great value in limiting such bacterial invasion of the sac, following rupture, to the residual fluid and to the amniotic surface for a considerable period of time. The presence of bacterial invasion of the sac gives no clinical evidence of its presence for twenty-four hours or longer as a rule, but occasionally clinical reaction occurs much earlier. Microscopic evidence of inflammatory reaction in the membranes occurs very soon after such invasion takes place. Bacterial contamination of the amniotic sac rarely gives rise to serious or fatal postpartum infections in patients who deliver normally. They are, however, the most important factor in infection, usually of the peritoneal cavity, taking place after the performance of cesarean section. As evidence of the early bacterial invasion of the uterus during labor, Harris and Brown[9] were able to obtain positive cultures in forty-four out of fifty patients at the time of cesarean section, these patients having been in labor six hours or longer. Anaerobic organisms were present in 45 per cent of the positive cultures.

As labor continues, the dilatation of the cervix gives rise to diffuse hemorrhage and edema, and causes minute lacerations of this structure. Occasionally deep lacerations may occur spontaneously. During the second stage, particularly in primiparae, hemorrhage and varying degrees of injury may occur in the vaginal mucous membrane. At the time of delivery the perineum is frequently injured by laceration or episiotomy. These points of injury offer possible points of entry for pathogenic organisms.

During the third stage of labor the placenta commonly detaches itself during the first few contractions following the birth of the fetus. It is expelled in a variable length of time stripping the membranes away as it leaves the uterus. Even if the membranes are contaminated with vaginal organisms, the mechanism of separation prevents the surface of the upper uterine segment from becoming inoculated immediately with bacteria. The postpartum uterus offers an ideal nidus for infection. In addition to the cervical injuries previously mentioned, the lining of the entire cavity above the internal os represents an extensive wound without epithelial covering. It is lined by the shaggy remnants of the decidua

where the membranes have been stripped away. Opening on the surface are the stumps of the basal glands, and numerous severed lymphatics and blood vessels. The placental site is represented by a round elevated area on the surface of which can be found the openings of large sinuses, some empty, some containing blood clot. The uterus is actively relaxing and contracting. During the early puerperium necrosis and shedding of the surface decidual remnants take place and following this the endometrium regenerates rapidly so that by the tenth to twelfth day the epithelial lining of the uterus is restored. The placental site remains, gradually becoming smaller and more constricted at its base, until at about the seventh to eighth week postpartum it is cast off, accompanied by a variable amount of bleeding.[10] Extensive involution of the myometrium and vascular changes occur during this period.

While the lining of the upper segment should be sterile in the normal patient following the third stage, within a short time this area is invaded by organisms which are usually already present in the cervix and lower uterine segment. By the third day of the puerperium it is heavily contaminated.[11] In a group of thirty-seven afebrile postpartum patients, Douglas and Rhees[1] obtained 78.4 per cent positive cultures from the uterine cavity and found that 64.8 per cent of the cultures showed anaerobic streptococcus. Most of the remaining organisms belonged to the group commonly found in the normal vaginal flora. In the vast majority of patients this bacterial invasion gives no clinical evidence of its presence except for the lochial odor for which the putrefactive action of these organisms is responsible. These organisms rapidly disappear in normal patients as the endometrium regenerates. By the ninth day it has been shown that in 70 per cent of postpartum patients[12] the uterine cavity has become sterile.

Having considered normal pregnancy, labor and the puerperium as a nidus for infection, we may now review the pathological changes induced by infection and the pathways along which this process may spread.

Pathogenic organisms may gain entrance at any of the points of injury in the lower genital tract, almost always giving rise to localized wound infections in these areas. Rarely such an infection is serious in itself. One such patient has been seen with a suppurative thrombophlebitis originating from an infected perineum. She died of embolism and, at autopsy, the uterus and its vascular system were found to be free from

infection. Lacerations of the cervix may become infected and such infection may spread through lymphatics into the base of the broad ligament producing pelvic cellulitis. These types of infection are seldom serious except in that they may lead to infection of the uterus itself.

Infection of the uterine cavity by pathogenic organisms gives rise to the majority of puerperal infections and almost all of the fatal ones. The favorable field which this cavity presents has already been described. The arrival of such organisms sets up an acute inflammatory reaction which may remain limited to the decidual remnants. Deeper penetration of the uterine wall by such infection is favored by the multitude of open lymphatics and vessels. Invasion of the uterine wall and the character of the cellular reaction is also influenced by the type of organism present. An additional factor may lie in the contraction and relaxation of the puerperal uterus, an action which may serve to suck organisms into the open vessels.

Most of our pathological knowledge of this condition is derived from the study of autopsies performed on fatal cases in which the infection has spread far past the uterine walls. Holban and Koehler have analyzed a series of 163 such postmortems. Sixty-four of these occurred in postpartum cases; ninety-nine followed abortion. A summary of their findings by Eeles[13] presents an excellent rapid review of the pathological findings and their interpretation and may be summarized in part as follows: They show that infection usually starts within the uterus itself. The appearance of the interior of the uterus varies. In many cases (20 per cent) it is lined by a perfectly smooth normal-looking endometrium, with or without an apparently harmless piece of placenta attached to the wall; or it may show a patchy inflammation with fibrinous exudate not necessarily involving the retained piece of placenta or placental site. Again the entire endometrium may be covered with a purulent exudate beneath which ulcers extend deeply into the uterine wall, an extreme stage of septic endometritis; or again the uterus may be large, soft, and flabby, its ulcerated walls covered with ragged decomposing tags of endometrium, its cavity filled with dark green semifluid material with a foul odor. This has been called putrid endometritis. This is due to a secondary invasion of the uterus by anaerobes. All stages may be found between this and septic endometritis. While the putrid type is usually due to an infection with anaerobes and saprophytes and the septic to recognizably pathogenic organisms (the chief being streptococci), yet

mixed infection is apparently possible and frequent. The condition of the interior of the uterus does not always give the key to the character of the infection.

From this infected cavity the infection may spread in three different ways, either alone or combined with one another. These ways are: (a) by blood vessels (veins), (b) by lymphatics, (c) by the tubes to the peritoneal cavity. A combination of all these methods of spread occurred in 71 out of 163 cases. A combination of (a) and (b) is most common. Extension by (c) is more frequent after abortion than after full time labor.

Venous Extension: Spread by blood stream is quite common. In nineteen cases this type of spread alone occurred; in another thirty, the veins were involved but not alone. Infection spreads from the interior of the uterus through the veins of the uterine wall. On section the thick muscular wall frequently shows multiple small abscess cavities and the veins in its substance are large and contain fluid blood or infected thrombi. The process then reaches either the pampiniform plexus and the ovarian vein or the parametric venous plexus, the hypogastric vein and the common iliac vein. Which system of veins is affected depends upon the point of entry of the infection but no definite connection could be traced between any piece of placenta and the veins involved. When larger veins are cut open, the endothelial lining may merely be roughened, with perhaps a thrombus adhering to it or they may contain a bright red thrombus with specks of yellow pus throughout it; or they may be filled entirely with yellow green pus from which during life organisms could continually reach the circulation. Periphlebitis with abscess formation may occur at any point. These abscesses frequently involve the ovary or they may rupture into the peritoneum. If blood infection takes its own course, the next stage is the formation of metastases. They occur chiefly in the lungs, notably in the lower lobes. If an abscess reaches the pleura, it is likely to rupture and result in empyema. If the emboli are small, that is, composed of minute groups of bacteria, they are able to pass through the lungs and reach the left heart where they may cause endocarditis, or, passing still further on, give rise to multiple small abscesses in the cortex of the kidney and produce infarcts in the spleen. No case of spread of infection by the blood stream was found that did not have a definite phlebitis.

Lymphatic Extension: Lymphatic spread through the uterine wall

to the cellular tissue of the parametrium occurred in no less than 115 cases. In forty-eight this was the sole method of extension. The uterine wall in these cases is hard and occasionally shows abscesses, multiple or single, which may rupture and cause peritonitis. If this does not happen, the infection reaches the enormous plexus of lymphatics in the parametrium. Frequently a massive hard edema accompanied by leukocytes and the deposition of fibrin takes place in this tissue. Sometimes the spread is rapid with only minimal tissue reaction. As the process continues, this cellulitis may extend upward behind the peritoneum on either side of the vertebral column or behind the colon, until it reaches the diaphragm, where huge collections of pus may accumulate; these are difficult to diagnose. Organisms may reach the thoracic duct directly by spread along the main lymphatics. Thence they gain entrance into the superior vena cava and general circulation. The emboli in this type of case are usually microscopic clumps of organisms and lung complications are less common, endocarditis more so, than in the blood-borne cases which show changes in the serous cavities: i.e., meningitis with multiple abscesses in the pia mater, pericarditis, pleurisy, synovitis and peritonitis.

Spread by way of tubes: Fatal spread by the tubes alone is least common and is chiefly found in abortion cases. The cause of death is peritonitis. The tubes are reached by direct surface spread from the endometrium. The inflammatory process in these fatal cases always extends too rapidly to allow the fimbria to adhere and occlude the tube. There is no enlargement of the tubes beyond simple inflammatory swelling. General peritonitis results and is rapidly fatal.

General peritonitis in puerperal patients is particularly fatal and it is not surprising that operation is usually hopeless in view of the postmortem findings. Though many cases are of the diffuse purulent type, the loculated form is more frequent. Coils of intestine are glued together with abscess cavities in between; into these the bowel may rupture or abscesses form between the ascending and descending colon and the abdominal wall and, spreading upward, form huge subphrenic abscesses. The lymphatic form, when peritonitis is present, is rapidly fatal. Peritonitis may be associated with any of the forms of spread and was present in 69 of 163 cases.

Martland[14] has analyzed the findings on 105 criminal abortions and has stated the cause of death to be peritonitis in 50 per cent, thrombo-

phlebitis in 31.4 per cent, and putrid endometritis in 7.6 per cent. The remainder died of an embolism or hemorrhage. His interpretation of the routes of spread are in the main similar to that set forth by Holban and Koehler. He also mentions direct extension of infection from the uterus to the peritoneum by perforating wound of the uterus. Such direct extension of infection is also responsible for peritonitis following cesarean section. It is usually immediate although it may occur some time after operation, due to disruption of the uterine wound. These represent the findings in the terminal stages of infection spreading from the uterus along various pathways in the relatively few fatal cases. One must remember that the spread of infection along these routes frequently is halted before reaching such proportions. Pelvic cellulitis without peritonitis or septicemia presents a favorable outlook. Many patients who present clinical evidence of thrombophlebitis recover.

Bacteriological investigation of patients with puerperal infection may be carried out by aerobic and anaerobic cultural studies of the uterine or vaginal discharges and of the blood. In the vast majority of instances, particularly in the milder forms of infection, such studies lead to confusing results. Most blood cultures are negative. The vaginal and uterine cultures often show a mixed group of organisms, many of which are similar to those found normally in the vagina. When a positive blood culture has been obtained one can be sure that one has identified the causative organism. When an organism is predominant or is present in pure culture in material taken from the vagina or uterus, this again is evidence, somewhat less strong, that the invader has been identified. Such positive findings are usually made in the more severe infections but even here one may fail to isolate the causative organism.

The organisms which are responsible most frequently for the more severe grades of puerperal infection are the streptococci, of which there are both aerobic and anaerobic varieties. Of the aerobic organisms some are non-pathogenic, others of mild virulence, while still others are the most rapidly invasive organisms known. After many attempts at classification a satisfactory method has been worked out. These organisms may be divided into alpha, beta, and gamma varieties on their cultural characteristics as grown on a blood agar plate. The alpha variety represents the organisms, such as Streptococcus viridans, which produce partial hemolysis; beta, those organisms producing complete hemolysis; and gamma, indifferent organisms producing no hemolysis.[15, 16]

Alpha and gamma varieties rarely are found in pure culture in the uterine or vaginal secretions and are usually associated with other organisms. Both types of organisms may be found among the normal vaginal flora. The Streptococcus viridans is associated with localized uterine infections and shows no marked invasive qualities. Occasionally it may set up a bacterial endocarditis in the wake of a puerperal infection, usually of the postabortal type. One severe and rapidly progressive infection caused by this organism has been seen on the wards at Bellevue Hospital, the patient dying of general peritonitis and septicemia following an induced abortion. At autopsy no endocarditis was found.

The most important organisms are the beta-hemolytic streptococci, not only in puerperal infection, but in human infection in general. These organisms have been classified into nine groups known as A, B, C, D, E, F, G, H and K, by Lancefield[17] by means of a precipitin reaction. Applying this to a large number of hemolytic streptococci obtained from various types of human infections, it has been found that practically all of these organisms belong to Group A. In a few instances other groups such as B, C, D, and G have been found to be the infecting organism. Furthermore, it is possible to break down the groups into a number of different types by agglutination. Among the strains belonging to Group A, twenty-three different types have been found.[18]

The application of this method of classification to hemolytic streptococci obtained from puerperal infection has confirmed many old impressions and has yielded most important facts. As has been stated before, this method has shown that Group A organisms do not and probably cannot exist in the vagina under normal circumstances. Other studies have shown that almost 100 per cent of the beta-hemolytic streptococci recovered from puerperal infections belong to Group A.[6] In a few instances other groups are found to be responsible, particularly Group B. These infections are usually mild although fatal infections are reported.[19] Group A beta-streptococci have been recovered from the air and dust in the vicinity of infected patients.[20] They have been found present in the nasopharynx of a considerable percentage of normal individuals, and in a much higher percentage[21] of individuals during or following acute pharyngeal infections. Finally in the majority of Group A infections investigated serologically, identical organisms have been found in the nasopharynx of an attendant, the patient herself, or in some other septic focus. [22, 23]

The significance of these findings may be briefly summarized as follows: Hemolytic streptococcus infections in the puerperal woman result from the introduction of an organism from Group A into the genital tract, almost always during labor and sometimes during the puerperium, from an outside source. This source may lie in the attendants, the patient, or in the surroundings of the patient. These infections may be called exogenous.

One may add a few words as to the behavior of these organisms in vivo. While less virulent strains tend to produce localized infections, the more virulent strains rapidly invade the lymphatic system and give rise to the fulminating sepsis, termed by Martland,[14] "uterine erysipelas." Menkin[24] has shown that this characteristic is due to the lack of any localizing defense mechanism for forty hours, such as is found with staphylococcus infections where an immediate production of fibrin plugs in the lymphatics, coagulation of plasma and edema localize the organisms. This quality may be related to the production of fibrinolysin by the streptococcus.[25] Certainly experimental studies and clinical experience would lead one to believe that this organism tends to spread chiefly by lymphatics. That this is not universally true can be shown by the fact that venous involvement in streptococcus infections is noted quite frequently. It is believed that the severity of infection with this organism is due to the virulence of the strain rather than any immunological weakness in the individual attacked.[26]

While this method of classification of the beta-streptococcus has been invaluable in making clear these facts, there are few institutions in this country where the technical assistance is available to carry out those complex procedures. From a practical point of view such cases can be discovered very rapidly by culture of the lochia on blood agar plates. Characteristic minute colonies surrounded by a wide zone of hemolysis appear within 12 to 16 hours, when the plates may be read grossly, the findings being later confirmed by microscopic examination. When such organisms are predominant or in pure culture and the patient shows a marked febrile reaction, one may be almost sure that one is dealing with a Group A beta-streptococcus and act accordingly. On the other hand when such colonies are present as a minority in the presence of many other organisms, febrile reaction in the patient usually is absent or present to slight degree. It is almost likely that these organisms belong to other groups than A. Positive blood cultures are only

obtained in serious infections and practically always indicate a Group A infection.

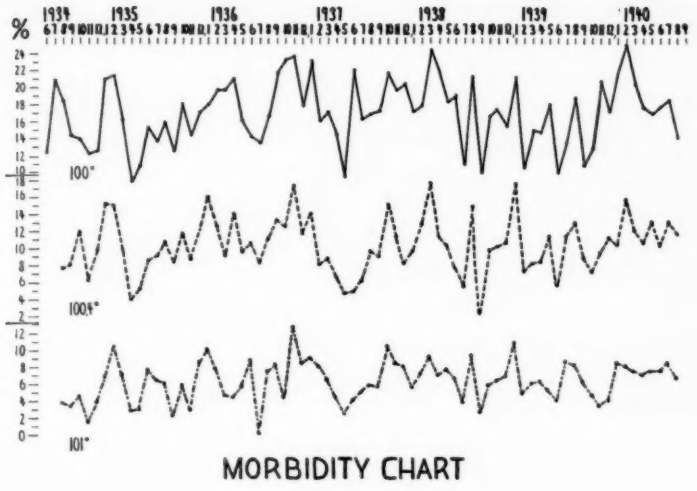
While Group A beta-streptococcus is the cause of severe sporadic puerperal infection and probably all epidemic puerperal infections, at the present time it is uncommonly the cause of such infection in New York City. Since 1933, 2600 lochial cultures have been taken on the Obstetrical Service at Bellevue Hospital from patients with fever or suspected infection. Sixty-nine of these cultures showed hemolytic streptococci, an incidence of 2.7 per cent. In only thirty-five of these cultures were hemolytic streptococci the predominating organism. On the Gynecological Service 622 cervical cultures were taken from patients suffering from abortion complicated by fever. Eighteen of these cultures or 2.9 per cent showed hemolytic streptococci. These organisms were not classified. Many of these patients showed no clinical evidence of the presence of a virulent organism, showing no fever or fever of slight degree and short duration. We feel justified in assuming that the incidence of Group A infections must fall well below 1 per cent. Watson states that only one severe Group A infection has been seen at the Sloane Hospital since 1936.[27] Douglas[28] states that beta-hemolytic streptococcus was found in only 1 per cent of the morbid patients at the New York Lying-In Hospital. While such infections are rare at present, there is no reason to think that this state of affairs is permanent, since the incidence may show a sharp increase at any time.

The anaerobic streptococci represent a group of organisms made up of a large number of strains. Attempts to classify these organisms with serological or biochemical methods have met with failure.[29] They can be classified by their cultural characteristics and gas production into four types.[30] This classification, however, has no particular clinical significance. They are strict anaerobes and anaerobic methods must be used to grow them in uterine or lochial cultures. The obtaining of positive cultures from these sources has no significance since they are present with a high degree of frequency in the normal vagina before labor,[2, 3] in the normal uterus postpartum[1] and in the same locations in febrile cases.[1] Attempts to prove the pathogenicity of these organisms has generally met with failure.[31] It is, therefore, impossible to investigate the nature of this infection from an experimental point of view. Somner[32] believes that the invasion begins by lymphatic spread. This is followed by involvement of the vein walls and, as a result of this, venous throm-

bosis. This belief is borne out by the moderate parametritis present in thrombophlebitis and by the microscopic appearance of the involved veins. In spite of lack of proof, an increasing number of observers are convinced that these organisms are responsible for a large proportion of puerperal infections.[30, 33, 34, 35] This conviction is based on the fairly frequent occurrence of cases of suppurative thrombophlebitis of the uterine veins accompanied by a bacteriemia with these organisms and the production of metastatic abscesses, chiefly in the lungs. It must be emphasized that special anaerobic methods[30] must be used to grow these organisms from the blood. While the factors which cause these organisms to take on pathogenic qualities are at present unknown, it is possible that trauma may contribute since most patients showing this type of infection have had mechanical interference in the delivery of the fetus. Since the source of this infection lies almost certainly in the vaginal tract it may be properly called an endogenous infection.

While the above-mentioned organisms are probably the chief offenders, nevertheless, one must remember that puerperal infection may be caused by many other bacteria. The colon bacillus may be causative and is usually introduced by fecal contamination of the genital tract or because of an accompanying urinary infection. Such infections are usually local although occasional cases of bacteriemia are observed. Even when this organism appears in the blood stream, spontaneous recovery occurs as a rule. Gonococcus is a fairly frequent cause of puerperal fever, the spread of infection upward from the cervix being favored by labor and the postpartum state. These infections follow the characteristic course of gonorrheal salpingitis. Staphylococcus infections are usually local but occasionally severe spreading infections develop with bacteriemia and multiple embolic abscesses Pneumococcus, gas bacillus, and B. typhosus infections are occasionally seen. All of them are probably conveyed to the vaginal tract during labor and delivery. The source of the pneumococcus in the primary type of infection must undoubtedly be from the nasopharynx of patient or attendant. In the secondary type, it is metastatic from a pneumonia. Infections by the last two organisms result almost certainly from fecal contamination of the vaginal tract.

The incidence of puerperal infection is usually determined by calculating the incidence of fever postpartum. Since variations in standards and other factors make the exact determination of general incidence



MORBIDITY CHART

Chart I

difficult, figures from the Obstetrical Service at Bellevue Hospital will be quoted. The standard of morbidity used is based upon a fever of 100.4° F. or more, persisting over twenty-four hours during the puerperium, excluding the first twenty-four hours after delivery. While this includes patients with fever due to other causes than genital tract infection, estimated to be from 10 to 20 per cent, it fails to include many mild febrile reactions due to genital infection. It may, therefore, be considered a fair rough estimate of the incidence of puerperal infection. In 11,400 patients delivered since 1933 the average incidence of fever of this degree has been 10.5 per cent. Chart I shows a graphic representation of the month by month variation of morbidity calculated on this standard as well as on similar standards based on 100° F. and 101° F. fever. It will be seen that the majority of these fevers are slight, only about 4 to 6 per cent of the patients showing fevers of 101°. It may also be noted that there is no marked evidence of seasonal variation although in some years the morbidity appears to be greater in the winter and spring months. This is in marked contrast to the severe hemolytic streptococcus infections observed on the Obstetrical Service and on the Gynecological Service following full term pregnancy and abortion. Those have invariably occurred between late November and early May. This corre-

sponds with the seasonal incidence of other hemolytic streptococcus infections, particularly of the nose and throat. This relationship may be taken as additional evidence of the almost certain source of these infections. Applying the stated standard of morbidity to this group, we find that 1180 patients had postpartum fever. The vast majority of these patients had fever of slight degree and short duration. No clinical evidence was present of spread of infection past the uterus. Even in severe infections only a minority gave any clinical evidence of spread. Relatively few could be classed as spreading infections. It is of interest here to note that Rivett[36] in an analysis of 533 severe cases found that 57 per cent appeared to be infections localized to the uterus.

During this same period there occurred fifty-three deaths, an incidence of 4.65 per thousand delivered patients. Seventeen of these deaths or 32 per cent were due to infection, an incidence of deaths from infection of 1.5 per thousand delivered patients.

Of the seventeen deaths, five occurred in patients delivered by cesarean section. All of them had general peritonitis, which began either immediately following operation or after a lapse of several days during which time there was evidence of a severe uterine infection.

Excluding the latter cases, there were twelve deaths among the vaginal deliveries. Among these is one patient with primary pneumococcus infection of the uterus with bacteriemia and meningitis. Another showed a Staphylococcus aureus infection, bacteriemia apparently arising from a thrombophlebitis of the arm on the seventh day postpartum in a patient who had a cesarean and hysterectomy for accidental hemorrhage. She had multiple transfusions, infection gaining entrance through one of these small wounds. Autopsy revealed a bacterial endocarditis. Two patients showed general peritonitis and bacteriemia due to hemolytic streptococcus, the former diagnosis being verified at autopsy in one instance and at laparotomy in the other. Two patients did not come to autopsy. In one the exact type of sepsis is unknown. The other showed clinical evidence of a suppurative thrombophlebitis with no demonstrable bacteriemia. Autopsy was performed on the remaining six cases. Two showed gangrenous endometritis and associated suppurative thrombophlebitis, while three showed suppurative thrombophlebitis, the uterus appearing comparatively normal. In two of these cases an anaerobic streptococcus bacteriemia was demonstrated, and this organism was suspected as a causative agent in the other three. All of these patients

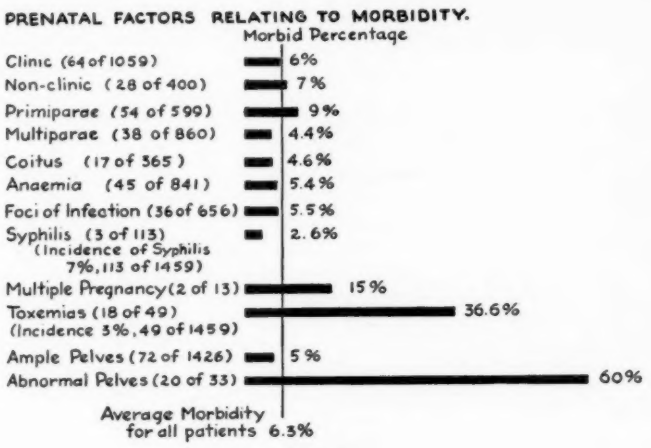


Chart II

showed pulmonary emboli or infarcts. In the last, the patient died a few hours after a long dry labor with intrapartum fever. She had an acute exacerbation of fever following delivery. Autopsy revealed nothing unusual but the blood cultures taken before death showed anaerobic streptococcus. The labors in the last group of six patients were marked by length, premature rupture of the membranes, amniotic sac infection, instrumental delivery, manual removal of the placenta, and tamponade of the uterus. Only one patient had a normal labor and delivery. Her infection was undoubtedly influenced by a pad accidentally left in the vagina. Rivett[36] has called attention to the high incidence of obstetrical interference in postpartum patients showing anaerobic streptococcus bacteriemia.

A group of these patients having a fever of 101° or more in the postpartum period have been analyzed by George Bowen in an endeavor to bring out factors occurring during pregnancy and labor which may be related to the appearance of postpartum fever. Chart II shows the antepartum factors. It will be seen that there is little difference between the patient who attends clinic and the one who does not. Primiparae show a higher incidence of fever than multiparae which may be related to the longer labor and the greater degree of trauma. A rather startling increase occurs among toxemias which may have some relation to their general condition and to a high incidence of interference. Patients with

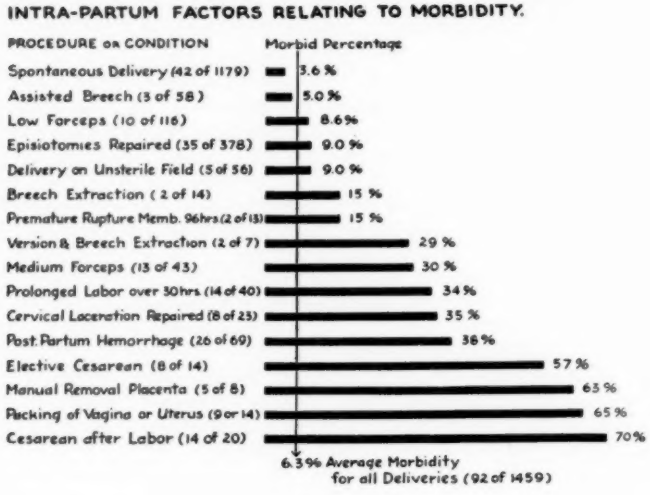

INTRA-PARTUM FACTORS RELATING TO MORBIDITY.
PROCEDURE or CONDITION
Morbid Percentage
Spontaneous Delivery (42 of 1179) 3.6 %
Assisted Breech (3 of 58) 5.0 %
Low Forceps (10 of 116) 8.6 %
Episiotomies Repaired (35 of 378) 9.0 %
Delivery on Unsterile Field (5 of 56) 9.0 %
Breech Extraction (2 of 14) 15 %
Premature Rupture Memb. 96hrs (2 of 13) 15 %
Version & Breech Extraction (2 of 7) 29 %
Medium Forceps (13 of 43) 30 %
Prolonged Labor over 30hrs (14 of 40) 34 %
Cervical Laceration Repaired (8 of 23) 35 %
Post Partum Hemorrhage (26 of 69) 38 %
Elective Cesarean (8 of 14) 57 %
Manual Removal Placenta (5 of 8) 63 %
Packing of Vagina or Uterus (9 or 14) 65 %
Cesarean after Labor (14 of 20) 70 %
6.3% Average Morbidity
for all Deliveries (92 of 1459)

Chart III

abnormal pelves show a very high rate probably due to prolonged labor and the high frequency of difficult operative deliveries. Chart III shows the intrapartum factors. It can be easily seen that with the exception of low forceps and breech extraction, all operative manipulation is accompanied by a great increase in morbidity. One cannot lay all the responsibility for fever on these procedures alone. Strict indications are laid down for their performance and in many cases the additional factors of prolonged labor, amniotic sac infection, and trauma, contribute to this increase.

This brief summary of the pathological and bacteriological features of puerperal infection, tinctured with some data on the background, incidence, severity and mortality gives us the fundamentals on which methods of prevention and treatment can be based. A consideration of these methods must be limited in this presentation to general principles.

Prevention is by far the more important field since by it alone are we likely to diminish the incidence and mortality due to postpartum infection. While difficult to prove, it seems quite obvious the pregnant woman in a perfect state of health at the onset of labor should be more resistant to infection than the women suffering from anemia, pyelitis, toxemia and other common antepartum complications. Close ob-

servation during pregnancy should lead to the control of many of these conditions. Careful study of the characteristics of the pelvis, and as a consequence, the consideration of possible difficulties during labor, should lead to an earlier decision as to whether certain patients should be delivered by cesarean section or allowed to go through labor. Here the various techniques of Roentgen pelvimetry are becoming of great aid to clinical judgment, particularly when utilized during labor. In other words, adequate antepartum care must play a part in the reduction of infection.

Since it must be generally admitted that most obstetrical patients suffering from complications of pregnancy and labor can be handled more efficiently and, as a rule, more safely in hospitals, a word may be said in regard to such institutions. Ideally an obstetrical hospital should be an entirely separate unit, with adequate facilities for completely separating patients showing evidence of postpartum infection from those who do not. The mingling of normal postpartum obstetrical patients with those suffering from general surgical and medical conditions is indefensible. When an obstetrical service is conducted as part of a general hospital, it should be placed in a part of the institution as remote as possible from wards containing patients suffering from acute infectious diseases. To send a patient to an institution which does not observe this fundamental in obstetrical organization is to invite infection.

Because the sources of infection are varied, it is obvious that the routes of infection and the methods of prevention must be different. As has been pointed out before, the sources of puerperal infection may be classed as exogenous and endogenous. The recent bacteriological studies lead to a clear-cut conception regarding prevention of the exogenous type, the commonest forms of which are caused by Group A beta-streptococcus and B. coli. They must be considered separately.

The principal sources from which Group A strains are derived in puerperal cases are from the nasopharynx of attendants or of the woman herself and from septic foci in fellow patients, members of the family, or herself. The source of such organisms and the method of transmission to the genital tract have been classified by Hare[4] as follows:

A. Organisms derived from a preëxisting infection in the neighborhood of the patient.

   Transmitted by air-borne infection; by instruments or hands; by infection of the nasopharynx of the patient and transfer as under

C; by contamination of hands of patient touching vulva.

B. Organisms derived from the nasopharynx of an attendant.
Transmitted by direct droplet infection; by direct droplet infection of the hands of the patient; by direct droplet infection of the throat of the patient and transfer as under C to the genital tract.

C. Organisms derived from the nasopharynx of the patient herself.
Transmitted by contamination of the hands touching vulva; by passage of organisms to the feces and subsequent contamination of the vulva during delivery; by passage of organisms by way of blood stream to placental site; by contamination of air and dust and transfer by air currents.

D. Organisms derived from hands of the attendant.
Transmitted by direct transfer to vulva.

E. Organisms derived from the hands of the patient.
Transmitted by direct transfer to vulva.

It should be obvious since the above sources and methods of transmission are capable of demonstration, that an obstetrical technique can be devised to block this type of infection. The cardinal points of such a technique are that (1) delivery should be carried out in an environment free from infection; (2) doctors and nurses should refrain from practicing obstetrics when suffering from acute nasopharyngeal infections of any sort; (3) droplet infection from the nasopharynx of carriers to hand or vulva should be minimized by the adequate masking of both nose and mouth of all attendants during labor, delivery and the early puerperium; (4) scrupulous attention should be paid to surgical technique by both nurse and doctor during labor and delivery; and (5) patients should be warned against touching the vulva.

These same principals apply equally well to the prevention of the much rarer primary pneumococcus infections.

The prophylactic use of sulfanilamide in patients at term has been suggested and there is experimental evidence to show that it may be of value.[37] The infrequency with which Group A infections are encountered in this vicinity leads to the conclusion that this measure would not be practical under the present circumstances. The prophylactic use of this drug under epidemic conditions or in individuals who have been exposed to such infection when close to term is another matter. Here it may prove of great value.

The prevention of B. coli infections would appear to be mainly

one involving: (a) the clearing up of urinary infections during pregnancy—sulfanilamide and the related drugs have proved of great value in accomplishing this end;[38] (b) an adequate preparation of the vulva before delivery, maintenance of an empty rectum during labor, and care to avoid contamination of the vulva with feces during delivery. Since the gas bacillus is also derived from the feces, this last group of measures applies as well to the prevention of infections by this organism.

While the principals of prevention in exogenous infections are quite definite, it is much more difficult to devise means of prevention of endogenous infections. The principal organism associated with this type of infection is the anaerobic streptococcus. As has been pointed out, these organisms are present in the vaginal tract of a large percentage of normal women before delivery, and in most instances, they give no evidence of pathogenicity in the postpartum period. Infections with this organism follow most often a prolonged exhausting labor, often with ruptured membranes, and usually terminated by difficult operative procedures. Two possible measures of prevention have been suggested. Careful antepartum study should anticipate a certain proportion of such labors and should lead to the decision to deliver the patient by cesarean section rather than by the vaginal route. It should be remembered, however, that such labors do not result merely from defects of the bony pelvis but also from variation in the soft parts, deficient pains and abnormalities of fetal presentation. Such a measure of prevention is easier to outline in theory than to put in practice. Early decision during labor as to the method of delivery and the choice of the proper type of cesarean section will minimize the danger of operation.

Another measure of prevention consists in the attempt to sterilize the vaginal tract during labor by various agents. Mayes[39] states that a marked lowering in morbidity has followed the use of mercurochrome instillations during labor. It has been shown that mercurochrome, merthiolate and other drugs markedly diminish the number of vaginal organisms.[40] Colebrook[41] confirms this observation using a number of antiseptics; he points out, however, that the organisms rapidly reappear and that the new flora contains many organisms not present before. He feels that the use of such agents is of no value, and since they may injure the defense mechanisms of the vaginal mucous membrane, they may be harmful. On the other hand Brown[42] reports that when vaginal instillations of acriflavine and glycerine are employed during la-

bor, there is a marked drop in positive cultures obtained from the lower uterine segment of those patients coming to cesarean section. As compared to an untreated series with 44 per cent positive cultures, he was able to show only 4.2 per cent. We have had no experience with the use of vaginal antiseptics during labor at Bellevue Hospital but feel that they may prove of value in diminishing the number of endogenous infections. This group of infections present a host of unsolved problems to the investigator. Until some of them are solved, these infections cannot be controlled.

In conclusion let us consider the influence of pathological and bacteriological studies on the treatment of infection after it has taken place. Such treatment can be considered under two heads, surgical and medical. Surgical therapy involves relatively few procedures, the most important of which consist of hysterectomy, ligation of veins draining the uterus, drainage of peritonitis, drainage of parametrial abscesses and the removal of retained secundines. The inadequacy of some of these procedures, as shown on the autopsy table, together with the marked tendency of the individual to localize infection spontaneously and to recover, has led to the abandonment of some of these procedures. Hysterectomy is rarely performed in these patients and in the records of Bellevue Hospital for the past seven years only one such operation has been done for this indication. The patient had a degenerating fibroid, infected with Staphylococcus aureus, and recovered promptly after operation. After a trial, ligation of thrombosed veins has been abandoned because of the uncertainty as to the exact point to be attacked and because of dubious results. Most authorities advise against the drainage of general peritonitis arising from a uterine focus. Our own experience at Bellevue leads us to believe that this operation tends to hasten the fatal termination. Surgical intervention at present is limited to the drainage of localized peritoneal exudates and of parametrial abscesses. The latter procedure is particularly effective and usually leads to rapid recovery. Finally, one may mention the removal of retained placental fragments. These fragments are present far more often after early abortion than after full term delivery, and the factor of infection frequently complicates their presence. Many authorities urge extreme conservatism until all clinical evidence of infection has subsided for some time before resorting to surgical removal. On the other hand, the removal of these fragments from patients showing clinical evidence of a localized infec-

tion with organisms of low pathogenicity is followed by rapid recovery in most instances.[43] Such cases infected with Group A streptococci should receive chemotherapy as a preliminary to the surgical procedure.

The main features of general care of these patients consist in complete bedrest, fresh air, sunlight, ample diet, and expert nursing attention. The gastrointestinal disturbances secondary to a spreading pelvic infection may make necessary suction drainage of the stomach and intestinal tract and the use of parenteral fluids containing glucose and electrolytes. The marked anemia frequently observed in these infections must be combatted with repeated transfusions. Less effort is expended in the elimination of pelvic exudates since it has come to be realized that both the process of parametritis and of thrombophlebitis represent important defensive mechanisms which tend to limit the spread of organisms. Once the spread is limited and the full defense of the patient is mobilized, such exudates tend to disappear spontaneously, providing abscess formation does not take place. Patients seen a year after recovery from the most severe pyogenic puerperal infection rarely show on examination any evidence of any residual lesion.

In addition to the general care of the patient, many special forms of therapy have been employed in these infections. Vaccines, serums, and a host of drugs have been used only to be discarded as valueless. The advent of sulfanilamide and its related compounds is, therefore, a great advance.

However, it must be pointed out that these drugs are only of value in certain types of infection which, at present, constitute only a small percentage of the total number occurring in this region. To use them rationally an early diagnosis must be made as to the nature of the invading organisms. As has been pointed out before, this can only be done on the basis of a positive blood culture or on the finding of a predominant organism in the lochial or uterine culture. In the majority of instances, blood cultures are sterile and lochial and uterine cultures show a mixed group of organisms. The most frequent bacteriemia observed in these patients at Bellevue Hospital is that caused by the anaerobic streptococcus; the second most frequent, that caused by the beta-hemolytic streptococcus. Colebrook reverses this frequency in his reports, which deal of course with much larger groups of cases.[30] Bacteriemias caused by primary pneumococcus, by staphylococcus, by colon bacillus and by gas bacillus infections are rare. The beta-hemolytic

streptococcus is the commonest clear-cut infection to be detected by means of lochial or uterine cultures. As has been noted, it is rarely found at the present time. Gonorrheal infections are usually disclosed by the examination of direct smears from the cervix and urethra. Cultural methods are available, are more efficient, but have not yet proved suitable for use as a routine diagnostic measure.

Considering the value of chemotherapy on such infections, it may be stated, from the clinical and laboratory experience of the past few years, that such treatment is of great value in puerperal infections caused by the beta-hemolytic streptococcus, pneumococcus, staphylococcus and gonococcus. Such treatment has proved of no value in genital infections caused by the anaerobic streptococcus and colon bacillus. Doubt has recently been expressed as to the value of chemotherapy in gas bacillus infections.[44]

The most important group of infections affected by these drugs is that caused by the beta-hemolytic streptococcus. One can classify patients showing this infecting organism into four groups: (a) Patients with positive cultures and no evidence of disease; (b) those showing positive cultures and slight degrees of fever; (c) those showing positive cultures, high fever but no evidence of spread past the uterus; and (d) those showing positive cultures, high fever, bacteriemia and other evidences of spread past the uterus. The latter types of cases may be called severe local and severe spreading infections. Chemotherapy should be limited to these two groups. Colebrook[45] reports a mortality of 22.8 per cent in patients with this degree of infection from 1930 to 1935. Since the advent of sulfanilamide this mortality has been reduced to 5.5 per cent. There are no reports in this country that can be compared to his, since no one observer has treated such numbers of this infection. Some idea of the infrequency with which severe infections with this organism are encountered at present may be gathered from the fact that in spite of careful search, one year elapsed before finding a severe hemolytic streptococcus puerperal infection at Bellevue Hospital to treat with sulfanilamide. Since this time we have seen eight cases of postpartum or postabortal sepsis with bacteriemia caused by this organism, all of whom have been treated with sulfanilamide. Five recovered and three died, a mortality of 37.4 per cent. Between January 1, 1933, and September 1, 1936, twelve such cases were admitted. Ten of these patients died, the mortality for the group being 83.3 per cent. While this

is a small series, nevertheless it shows a marked improvement in our results. Furthermore, all the patients with severe local infections have recovered and none have developed bacteriemia after treatment was begun. It is of interest that two of the patients who died showed suppurative thrombophlebitis of the pelvic veins and one, bacterial endocarditis. Lockwood[44] has pointed out that this type of lesion among others is not favorably affected by chemotherapy. Sulfanilamide, in our hands, has proved the most satisfactory drug for this type of infection. It can be used over long periods with relatively little disturbance of the patient. Time does not permit enlarging on the details of treatment which doubtless will be taken up by other speakers at this meeting.

A few brief remarks may be made on the other types of infection suitable for chemotherapy. Gonococcal infections respond readily in the majority of instances to sulfanilamide. In refractory cases additional treatment with sulfapyridine will often clear up this infection. The value of sulfapyridine in pneumococcus infections both with and without serum has been abundantly demonstrated and should be of value in both primary and secondary genital infections. We have had no experience in its use in primary infections. Sulfathiazole and sulfamethylthiazole appear to be better agents to use when staphylococcus infections are present. No opportunity for their use has presented itself at Bellevue, but I am acquainted with the details of one patient with puerperal septicemia in whom recovery took place under treatment with the latter drug.[46]

One can say, then, that the advances in chemotherapy have been of great assistance to the obstetrician in the treatment of a small group of cases caused by certain specific organisms. Fortunately, in this group we find infections of the most severe and fatal type, notably the Group A beta-streptococcus. In the vast majority of puerperal infections a mixed group of organisms is present. In a few of these cases we know, and in a large number we have cause to suspect that the anaerobic streptococcus plays a leading part. There is no known agent which affects favorably infections caused by this organism. This may well be due to the type of lesion produced which is, in a high proportion of cases, suppurative thrombophlebitis. Perhaps some future discovery will produce a successful agent against this type of infection. At present we must rely entirely on prevention to diminish its incidence, severity, and mortality.

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BRUCELLOSIS*

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BRUCELLOSIS (undulant fever, Malta fever, Mediterranean fever, goat fever, contagious or infectious abortion of cattle, Bang's disease, Texas fever, Rio Grande fever, et cetera) is now known to be a common and widely distributed disease of animals and man. Our studies of this disease, begun in 1928, resulted in the discovery of ninety cases in and about Dayton during a period of eighteen months. In 1930, the author expressed the belief that brucellosis would soon become recognized as a major public health problem. That this opinion was justified has been abundantly substantiated by developments of the past decade.

The first cases of Malta fever to be recognized in this country occurred among men recently returned from the Tropics (Musser and Sailer, 1899). Craig (1905) not only detected many cases among men in the Army who had served in the Philippine Islands, but also established the diagnosis in a nurse who had never been out of the country and who had had no contact with patients with Malta fever. Craig suggested at this time that many patients with atypical typhoid-like fever might be suffering from Malta fever. A few cases of the disease were reported from goat-raising areas in Texas, New Mexico and Arizona by Gentry and Ferenbaugh (1911) and by Yount and Looney (1913). Then the disease apparently faded from medical consciousness for a decade, when Lake and Watkins (1922) published their startling report of an epidemic of Malta fever in Phoenix, Arizona, which they traced to the infection of raw goat's milk. Up to this time physicians naturally associated brucellosis only with a goat source. It was the monumental observation by Alice Evans (1918), that the organisms of Malta fever and contagious abortion of cattle were for all practical purposes indistinguishable, that led to the discovery of the widespread occurrence of Brucella infection of bovine and porcine origin.

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Following the first report by Keefer (1924) of a case of brucellosis due to the abortus variety of the organism, a rapid succession of reports of cases of bovine or porcine origin appeared from South Africa, Canada, Germany, Sweden, Norway, Denmark, Italy, Great Britain, Switzerland, The Netherlands, France, Puerto Rico and New Zealand. Subsequent reports leave little doubt that brucellosis is world-wide in its distribution and is most prevalent in those areas in which Brucella infection of cattle, hogs and goats is widespread.

For twenty-one years the Micrococcus melitensis of Bruce and the Bacillus abortus of Bang had been regarded as separate, unrelated species, until Alice Evans' observation that the two organisms are indistinguishable morphologically, biochemically, culturally, and by ordinary agglutination tests. The results of further studies led Evans to state that the two organisms probably possessed similar pathogenicity for human subjects. In 1927, Carpenter recovered an organism indistinguishable from Brucella abortus from the blood of ten human beings suffering from brucellosis; five pregnant heifers inoculated with these cultures promptly aborted. These observations of Evans and Carpenter have been confirmed by many workers throughout the world. It is now known that the organism which produces contagious abortion in cattle and other domestic animals is capable of producing in human beings a disease clinically and bacteriologically similar to the Mediterranean type of Malta fever.

Since Bruce had described the organism as a coccus and Bang had termed it a bacillus, it became apparent that the melitensis-abortus group of organisms should be reclassified. The proposal by Meyer and Shaw that the organisms should be designated by the generic name Brucella has met with universal approval. Consistent with this proposal, the name Brucellosis has been generally adopted as the single designation for the disease produced in animals and man by the Brucella. The organism usually associated with goat infection is termed Brucella melitensis, while the organism of infectious abortion of cattle is called Brucella abortus. Traum described a third related organism associated with the infection in swine, which has been designated Brucella suis.

Organisms which have been designated as caprine (melitensis) or porcine (suis) have been recovered from cow's milk. The antigenic differences are probably best explained on the basis of host adaptation. It seems probable that Brucella abortus is the primitive strain from which

other strains have developed as the result of passage through various animal hosts.

The importance of brucellosis as a rapidly developing public health problem is vividly indicated by recent experiences with the disease in the United States. Prior to 1927, the sporadic cases which were encountered were regarded as clinical curiosities. Most of these were related to endemic foci of goat infection in Texas, New Mexico, and Arizona. During the years 1927 to 1930, the recorded cases numbered 217, 649, 1301 and 1385, respectively. During 1929, cases of brucellosis were encountered in every state of the Union. In 1940, 3358 cases were officially reported to the U. S. Public Health Service by State Health Departments. It is undoubtedly true that the number of cases actually occurring is much larger than that reported. Hardy reported the occurrence of 1669 cases in one state (Iowa) from 1925 to 1935. It has become more and more apparent that this rapid increase in the incidence of the disease has been due chiefly to infection of human beings with the organism of contagious abortion of cattle and hogs. American physicians soon realized that these observations provided an explanation for their failure to arrive at a confirmed diagnosis in many cases of typhoid-like and malaria-like diseases.

Among urban populations, the disease appears to be transmitted through the raw milk of cattle infected with Brucella abortus. Of the 220 patients with brucellosis studied personally by the writer, the ingestion of raw milk or unpasteurized dairy products containing the organism of contagious abortion of cattle was demonstrated to be the source of infection in the great majority of instances; these findings are corroborated by the investigations of Carpenter, King, Orr, Huddleson, Farbar, Mathews, Sensenich, Giordano, Ey and others. Hardy expresses the belief that direct contact with infected cattle and hogs has been responsible for a great number of cases of brucellosis occuring in Iowa. Hardy's investigations of 991 cases of brucellosis occurring in that State, led him to the conclusion that the abortus and suis species of the organism are about equally responsible for the brucellosis morbidity in the State. Hardy has demonstrated by animal experiments that the skin may act as the portal of entry of the organism. Morales-Otero, of Puerto Rico, has reproduced the disease in human volunteers by inoculations through abraded skin. It is apparent, therefore, that there are two important sources of infection for man, that is, the ingestion of raw milk

or unpasteurized dairy products containing Brucella, or direct contact with infected fresh animal tissues or discharges. There is no definite evidence of man-to-man transmission of the disease.

Clinical Manifestations in Man

Because brucellosis presents many symptoms and signs common to typhoid fever, malaria, tuberculosis and influenza, it is frequently confused with these diseases. Many physicians have arrived at a tardy diagnosis of brucellosis only after repeated negative Widal reactions, the failure to demonstrate the malarial plasmodium, and the inability to elicit physical signs or x-ray evidence of tuberculosis. Less often, the disease has been confused with acute rheumatic fever, subacute bacterial endocarditis, bronchitis, pyelitis, appendicitis, cholecystitis, or tularemia.

Symptomatology

As knowledge of the clinical manifestations of brucellosis has advanced, particularly during the past decade, it has become more and more apparent that the older text book descriptions of the symptomatology of the disease were based largely on experiences with brucellosis of goat origin. The classical clinical picture of a disease characterized by an undulatory, remittent, or intermittent fever, drenching sweats, chills, headache, backache, muscular and joint pains, weakness, loss of weight, possibly a palpable spleen, an infrequent skin eruption, leukopenia with lymphocytosis, and secondary anemia, pertains chiefly to the severe acute forms of the disease. In a high proportion of cases, the disease pursues a relatively mild, prolonged course, extending over many months or years. The early descriptions by Hughes and Craig included many such cases. Alice Evans and others have more recently directed particular attention to the common chronic ambulatory form of brucellosis in which the patient, whose spirits are already depressed by continued ill health, is often given further discouragement when a diagnosis of neurasthenia is made. Many "neurasthenics," whose chief complaints were exhaustion, insomnia, irritability, and a variety of aches and pains, have been found to be victims of chronic brucellosis.

Since the symptomatology of the acute and the chronic forms of brucellosis varies so greatly, these two manifestations will be considered separately.

Acute Brucellosis

The incubation period has been found to vary from five days to longer than one month. In accidental laboratory infections the incubation period has varied from ten to twenty days. The prodrome is not unlike that of any general infection, with a gradual onset, although in occasional cases the disease is initiated with a sharp chill and rapid elevation of temperature to 103-105 F. (39.4-40.6 C.). A sense of tiredness and weakness, loss of appetite, constipation, headache and backache are common early symptoms. Usually, the patient becomes gradually aware of an afternoon or evening rise in temperature, associated with chills or chilly sensations, nocturnal perspiration and weakness. The patient often feels quite well during the morning hours, particularly in the early stages of the infection. As the temperature rises, during the afternoon or evening, the symptoms gradually return and increase in severity. The nocturnal exacerbations of fever occasionally reach great heights (106-107 F.; 41.1-41.7 C.). There is often a remarkable disparity between the subjective sense of fever and the height of the fever as registered by the clinical thermometer; in many instances the patient does not complain of fever, nor does he present a febrile appearance, but the physician finds, to his surprise, a fever of 101-103 F. (38.3-39.4 C.). As the fever abates, chills and sweating occur. If defervescence is rapid, the perspiration is more likely to be of a drenching character. In such cases, the sweats, which literally saturate the night clothing and bedding, are one of the most impressive features of the disease. The perspiration often has a peculiar sweetish, fetid odor. The chills may be severe enough to be regarded as true rigors in about one-third of the acute cases. Many patients experience only mild chilly sensations, while in about one-fourth of cases chilliness is absent.

Arthralgia and muscular pains are prominent features of the acute form of the disease in approximately one-half of the cases. The joint pains may be more pronounced during the onset or they may persist throughout the course of illness. The myalgia may be accompanied by a feeling of "stiffness" not unlike the muscular soreness which follows vigorous exercise. Hydrarthrosis and transient periarticular swelling have been observed occasionally. Permanent impairment of the joints usually does not occur. Suppurative osteomyelitis as a complication of brucellosis has been described with increasing frequency during the past

few years. In most of the reported cases the vertebrae, particularly in the lumbar region, were attacked. In some instances other bones, such as the humerus, femur, skull and ribs, were affected. While the osteomyelitis sometimes occurred relatively early in the course of the disease, in most cases it was a late complication, occasionally occurring after apparent recovery from acute brucellosis. Feldman and Olson found similar examples of Brucella spondylitis in twenty-four hogs, an average occurrence of one in every 6000 swine slaughtered.

Marked restlessness and insomnia usually accompany the nocturnal febrile exacerbations. Delirium occurs in some cases in which the fever reaches great heights. Regional Brucella localizations in the brain, spinal cord or meninges may occur during the acute phase of the disease and produce symptoms and signs of encephalitis, myelitis or meningitis; such complications are, however, more commonly observed as delayed manifestations of brucellosis. According to Roger and Poursines, whose recent classical monograph has aroused great interest in the frequency of central nervous system invasion by Brucella, the meningeal involvement predominates, and the development of encephalitis or myelitis, or both, is usually secondary to the meningitis. Because of this predilection for meningeal localization, Roger and Poursines have termed this form of the disease "meningoneuro-brucellosis." The involvement of the central nervous system may produce the first and only symptoms of the disease. The symptomatology varies greatly, depending upon the extent of meningeal invasion and the presence of additional complications involving the brain, spinal cord or peripheral nerves. In a patient with brucellosis, the development of such symptoms and signs as severe headache, vertigo, diplopia, nuchal rigidity, aphasia, psychic disturbances and various forms of paralysis, which are often evanescent, calls for examination of the cerebrospinal fluid. Characteristically, the spinal fluid will be under increased pressure and will show pleocytosis, increase of albumin and a decrease of globulin and sugar. Since the ultimate diagnosis during life depends upon the isolation and identification of Brucella from the spinal fluid, a particularly diligent effort should be made to recover the organism by culture and by guinea pig inoculation. DeJong has recorded eleven verified cases of Brucella meningitis or meningoencephalitis in which the organism was recovered from the spinal fluid by culture or by guinea pig inoculation.

The matutinal remissions or intermissions and the nocturnal exacer-

bations of fever may last from one week to many months. The inadequate name "undulant fever" refers to recurring relapses of fever following afebrile intermissions. Such febrile relapses are the exception rather than the rule; most patients experience but one febrile period, lasting from a few days to several months, and finally reaching the normal level by lysis.

The essential gastrointestinal complaints are anorexia and constipation. The degree of constipation appears often to parallel the severity of the infection. Diarrhea is of rare occurrence. Nausea and vomiting may occur in the more severe cases. Abdominal pain is a not infrequent feature of the disease during its early manifestations. Among 125 cases studied by Hardy, abdominal pain occurred in forty; in ten it was the major complaint. Simpson found abdominal pain to be the chief complaint in sixteen of 142 patients with brucellosis. The occurrence of abdominal pain has often led to appendicectomy in patients with unsuspected brucellosis, the correct diagnosis having been made only after the persistence of febrile symptoms stimulated a further search for the cause. As in typhoid fever, the gall bladder may become a focus of Brucella infection. Brucella has been recovered from the excised gall bladder and from the bile following duodenal drainage in patients with symptoms of cholecystitis.

Symptoms referable to the respiratory tract may be an outstanding feature of the disease in certain instances. Cough, associated with mucoid or mucopurulent sputum production, is not infrequent during the first few weeks of illness, and may persist for months. Recent reports provide convincing evidence that pulmonary lesions of brucellosis are of frequent occurrence and are often detectable by roentgenographic examination, even in the absence of distinctive physical signs of pneumonia. The lesions most often encountered on x-ray examination are peribronchial infiltrations, hilar infiltrations, and scattered discrete or confluent patchy pneumonic areas. The pulmonary manifestations of brucellosis should be regarded as hematogenous lobular pneumonia rather than true bronchopneumonia. Without doubt, pulmonary lesions occur much more commonly than is generally realized. Serial roentgenographic studies will often provide an explanation for vague respiratory symptoms.

The most serious cardiovascular complication has been the occasional occurrence of vegetative endocarditis. Smith and Curtis found

reports of nine cases of Brucella endocarditis confirmed by postmortem examination, to which they added a similar case. In most instances the vegetations occurred on mitral or aortic valves previously damaged by rheumatic fever.

The name commonly applied to brucellosis of cattle, "infectious abortion," is derived from the well-known predilection of the causative organism for the genital tract. There is strong evidence that the same regional localization sometimes occurs in human beings. Painful swelling of the testes has been described frequently. Acute epididymitis, orchitis, prostatitis and seminal vesiculitis may be early manifestations of the disease. Simpson recovered Brucella abortus from a draining sinus tract which extended from the globus major of the epididymis through the scrotal wall.

There appears to be little doubt that brucellosis is at least an occasional cause of abortion in women who live on farms where they have direct contact with infected animals, or in women who consume raw milk or unpasteurized dairy products. There are reports of human abortion in which the history and serologic findings provide strong circumstantial evidence of the etiologic role of Brucella. In a study of 565 cases of brucellosis, Calder found a history of one or more miscarriages in 32 per cent of the married women; a history of one miscarriage followed by sterility was common; a few women reported as many as five or six abortions. More direct evidence has been provided by Carpenter and Boak who recovered Brucella abortus from the tissues of a human fetus which was aborted at the end of the fourth month of gestation. Kristensen isolated the abortus variety of the organism from the exudate which covered the uterine site of the placenta of a seven-month fetus. Frei isolated Brucella from the vaginal discharge of a woman who had aborted ten days previously.

Loss of weight is an almost constant feature of the acute form of the disease. The greatest loss, often from ten to fifty pounds, occurs in patients with high fever, drenching sweats and great prostration.

A transient cutaneous eruption, usually papular, macular or maculopapular, is a relatively infrequent finding. The skin lesions may simulate the roseola of typhoid fever.

Chronic Brucellosis

Many physicians feel that the symptoms and signs of acute brucel-

losis are often sufficiently characteristic to justify such a provisional diagnosis on the basis of clinical findings. In dealing with chronic brucellosis, however, the physician is often faced with a problem which will tax his diagnostic acumen to the utmost. No disease, not excepting syphilis and tuberculosis, is more protean in its manifestations.

Quite naturally, a certain amount of wholesome skepticism has arisen in the minds of some physicians regarding any wide prevalence of chronic brucellosis. Such a feeling of doubt is quite defensible, since one is justified in questioning the validity of some of the diagnostic tests upon which such a diagnosis is often based.

The common and unfortunate employment of the name "undulant fever" has served only to add further difficulties in the recognition of cases of chronic brucellosis. A significant temperature curve, physical signs of disease, and positive agglutination tests and skin tests may be entirely lacking throughout a long period of chronic illness. The recent studies by Evans, Poston, Angle, Scoville, Thames, Calder, Hamman and Wainwright, Harris, and Cameron and Wells leave little doubt that a protracted, relatively mild form of brucellosis is widely prevalent and constitutes a major cause of chronic ill health. Only a small proportion of patients with chronic brucellosis, probably less than 10 per cent, have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis. In many cases the patient is not entirely incapacitated for work, but complains chiefly of weakness and exhaustion, with or without mild fever. Since the commonly employed diagnostic tests are frequently negative in such cases, and since even the most conscientious physician may not find physical abnormalities to account for the patient's complaints, the almost inevitable diagnosis of neurasthenia or psychoneurosis is too often made.

Surveys conducted in widely separated parts of the United States during recent years reveal that an ambulatory, partially disabling, chronic form of brucellosis is a widespread cause of prolonged ill health. Angle, Algie, Baumgartner and Lunsford found that 9 per cent of 7,122 school children gave positive reactions to the intradermal test; 79.3 per cent of the positive reactors consumed raw milk; a high proportion of the children had complaints consistent with the ambulatory type of brucellosis. Gould and Huddleson observed positive reactions in 845 of 8,124 persons (10.3 per cent) tested intradermally with brucellergin. Most of these individuals were residents of an infirmary for homeless

indigents and of a mental hospital where unpasteurized milk was consumed and where the supply of dairy products was obtained partly from a herd known to be infected with Brucella. Of the 845 reactors to the skin test only 111 (13.1 per cent) showed a positive agglutination reaction. The unreliability of the agglutination test in detecting chronic brucellosis has been noted by many other workers.

A recitation of all of the symptoms which have been ascribed to chronic brucellosis would serve only to heighten the confusion which as yet surrounds this baffling phase of the disease. In general, it may be stated that the three cardinal features of most cases of chronic brucellosis are weakness, low-grade fever and a lack of objective physical findings. McGinty and Gambrell have listed over 150 different manifestations of chronic brucellosis. Mild degrees of fever may be present for many weeks or months; there may be several months of complete freedom from fever; sudden febrile exacerbations may occur, accompanied by an accentuation of the prevailing symptoms, or by the development of evidence of new regional symptoms affecting the respiratory, cardiovascular, genitourinary, gastrointestinal, skeletal or nervous systems. Pneumonia, endocarditis, orchitis, epididymitis, prostatitis, oöphoritis, cholecystitis, hydrarthrosis, arthritis, spondylitis, osteomyelitis, ocular complications or meningoencephalitis may be associated with the acute form of the disease, but much more commonly appear several months, or even years, after the often indefinite onset of the chronic form of brucellosis. In some instances such delayed evidences of regional Brucella localization may appear long after apparent recovery from the acute manifestations of the disease. All students of chronic brucellosis have emphasized the almost universal prominence of symptoms which relate to the central nervous system. In addition to the occasional acute invasion of the meninges, brain and spinal cord by Brucella, there is evidence that the endoantigen of Brucella organisms circulating in the blood has a toxic action upon the central nervous system. These observations led Evans to state: "These facts challenge the right of a physician to make a diagnosis of neurasthenia—a diagnosis regarded as dishonorable by the patient, and also by his family, his employer and his friends—without considering, among other possibilities, the possibility of chronic brucellosis."

Chronic brucellosis should be suspected in all cases of so-called "fever of unknown origin." There are many reports of the isolation

of Brucella from the blood, urine, bile or from extirpated tissues in patients who have experienced unexplained, long-continued, low-grade fever for years. Hamman and Wainwright reëxamined thirty-six such patients; an accurate diagnosis was finally made on ten of them; three were found to have brucellosis.

In contrast to acute brucellosis, it is of particular significance that chronic brucellosis has been recognized in relatively few areas in the United States. The discovery of a large number of cases in these centers has been largely the result of a determined effort on the part of a few investigators to learn of the incidence of the disease in their localities. It seems quite apparent that the vast majority of cases remain unrecognized, since the evidence at hand indicates that chronic brucellosis is widely prevalent in rural communities and in cities and towns in which raw milk is consumed.

Diagnosis

If brucellosis is given consideration in the differential diagnosis of all cases of febrile illness, especially in those in which the diagnostic criteria for typhoid fever, tuberculosis, influenza, malaria, chronic bronchitis, pyelitis, rheumatic fever or bacterial endocarditis are not convincing, the disease will be recognized with much greater frequency. This is true in cases of vague, mild febrile disease as well as in those in which the clinical manifestations of brucellosis are more clearly defined. In such cases it should become an established practice to submit 4 or 5 cc. of the patient's blood, collected exactly as for the Wassermann test, to a laboratory equipped with the proper Brucella antigens, for the agglutination test. The rapid macroscopic agglutination method of Huddleson is a simple and reliable procedure.

Since it is exceedingly hazardous to base a diagnosis of brucellosis solely on clinical grounds, recourse must be had to laboratory diagnostic tests. These procedures include (a) primary isolation of the causal organism by cultural methods from blood, spinal fluid, secretions, excretions, or excised tissues; (b) indirect recovery of Brucella by culture after animal inoculation; (c) the agglutination test; (d) the intradermal test; and (e) the opsonocytophagic reaction.

The only method by which the diagnosis of brucellosis may be completely established is by the *cultivation and identification of the organism.* While cultural techniques have improved greatly during the past

few years, with a corresponding increase in the number of reported instances of recovery of the organism, the undertaking is often beset with difficulties and requires skill and, above all, patience. The melitensis and suis varieties of Brucella ordinarily grow readily under aerobic conditions, while the much more commonly encountered abortus variety requires an atmosphere containing 10 per cent carbon dioxide. The procedure used by Poston with notable success is as follows: 15 cc. of blood are obtained from each patient by venipuncture and placed in a small flask containing 4 cc. of sterile 2.5 per cent sodium citrate solution. Four flasks containing 100 cc. of liver infusion broth of pH 6.8 are each inoculated with 2 cc. of the citrated blood. The flasks are incubated at 37 C., two in the room atmosphere and two in an atmosphere containing 10 per cent CO_2. After four days' incubation, daily smears of the broth cultures are made and stained by Gram's method. If no organisms are seen in the smears after ten days' incubation, 5 cc. of the original culture are transplanted to 100 cc. of liver infusion broth every three days for two weeks. Original cultures and transplants are incubated for three weeks before they are reported as negative.

The guinea pig is the most suitable laboratory animal for inoculation. Poston inoculates three guinea pigs with blood from each patient; two are injected intraperitoneally with 2 cc. each of citrated blood; one is inoculated in the groin with 1 cc. of citrated blood. The animals are observed daily. Beginning two months after inoculation, tests for specific agglutinins and for cutaneous reaction to Huddleson's brucellergin are made at intervals of a few days. When both tests become positive the animals are killed. Animals which remain negative to the agglutination test and to the skin test are killed four and one-half months after inoculation. Liver infusion broth is planted with the guinea pig's blood and with pieces of organs and is subjected to the cultural procedures previously described. The cultures may then be differentiated into abortus, suis or melitensis varieties by the agglutinin-absorption technique, the bacteriostatic action of dyes, glucose utilization and hydrogen sulphide metabolism.

The most commonly used and the most reliable indicator of Brucella infection, in the absence of positive cultures, is the agglutination test. This is particularly true in cases of acute brucellosis, in which a high serum agglutinin titer will be found in a great majority of cases. Agglutinins may appear as early as the fifth day of illness, but ordinarily

are not found until the second week after the onset. In some instances, specific agglutinins may not appear for several weeks. One important source of difficulty in interpreting the results of agglutination tests is the fact that agglutinins may be persistently absent (in about 6 per cent of patients) or may be present in low titer in persons from whom Brucella has been cultivated. Another source of error in interpreting the agglutination reaction is the fact that the titer may remain at a high level for months or years after recovery. Then, too, some individuals exposed to the infection may develop agglutinins without notable illness. Furthermore, the level of the agglutinin titer may fluctuate widely on repeated testing. *These considerations call for the exercise of keen judgment in interpreting the results of the agglutination test. A person suffering from some disease other than brucellosis may have a positive agglutination test merely as the result of a previous symptomatic or asymptomatic Brucella infection.*

In the past, diagnostic significance has usually been attributed to titers of 1:80 or above. The choice of such an arbitrary diagnostic titer is not justified in the light of recent studies. In those cases in which the clinical manifestations suggest brucellosis, the absence of agglutinins or their presence in titers of 1:10 to 1:40 should stimulate further bacteriologic and serologic studies.

The difficulties which attend the interpretation of agglutination tests in cases of acute brucellosis are greatly multiplied in cases of chronic brucellosis. While the great majority of patients with the acute form of the disease reveal a positive agglutination test in high titer, a high proportion of patients with chronic brucellosis give repeatedly negative agglutination reactions or positive tests in low titer. In a group of twenty-eight cases of chronic brucellosis studied by Evans, 46 per cent gave a negative agglutination reaction.

The occasional cross agglutination of *Brucella* and *Bacterium tularense* should be borne in mind. In cases of tularemia the relatively higher titer with the *B. tularense* antigen and the usually typical history leaves little doubt as to the interpretation of the serologic findings. If the *Brucella* and *B. tularense* titers are the same, or nearly so, agglutinin absorption tests will distinguish between them.

While the agglutination test is undoubtedly of great value, its limitations must be recognized. Otherwise, errors will be made in two directions: first, the correct diagnosis of brucellosis may not be made because

too much reliance is placed in a negative test; or second, an incorrect diagnosis of brucellosis may be made in a person who has a residual agglutinin titer from a previous invasion by Brucella, but who is suffering from some other disease when the test is made.

The *intradermal* test is used to determine cutaneous hypersensitiveness to specific Brucella antigen. A positive allergic skin reaction is generally accepted as evidence of past or present Brucella infection. While the great majority of patients from whose blood Brucella has been recovered show a positive skin test, the test has yielded negative results in rare instances in which Brucella infection was proved by culture.

The chief sources of error in interpreting the significance of a positive skin test lie in the fact that the test is frequently positive in exposed individuals with no history of an illness compatible with brucellosis. Furthermore, the hypersensitiveness, once acquired after symptomatic or subclinical infection, usually persists for many years. *Therefore, it must be emphasized that a positive skin test does not mean that the symptoms from which the patient is suffering at the time of a positive skin test are necessarily due to brucellosis.* Students of this disease are only too familiar with instances in which a diagnosis of brucellosis was made only on the basis of a positive skin test and in which further developments revealed the presence of some such disease as active tuberculosis, Hodgkins' disease, leukemia, typhoid fever, malaria, or subacute streptococcic endocarditis. The intradermal test is regarded by Evans as a less accurate indicator of present infection than the agglutination test because the allergic state usually develops later than agglutinins and because it is generally retained for longer periods after recovery. Gould and Huddleson regard the skin test as the most sensitive diagnostic test for brucellosis; these investigators express the belief, shared by many others, that if the skin test is negative, brucellosis may usually be ruled out.

A variety of antigens has been used for skin testing. The two agents most commonly employed are (1) a heat-killed suspension of Brucella in physiologic saline solution (vaccine) and (2) a suspensoid of nucleoprotein isolated from Brucella by chemical separation, known as Brucellergin (Huddleson). If commercially available vaccines are used for skin testing, the usual procedure is to dilute the vaccine in a proportion of one part vaccine to nine parts sterile physiologic solution of sodium chloride and to inject 0.1 cc. of the diluted suspension intracutaneously in the ventral surface of the forearm. It is important to select properly

standardized vaccines from a reliable source. Variations in the manner of preparation, potency and dosage have led to a lack of uniformity in the production and interpretation of cutaneous reactions. Brucellergin has the advantage of being a standardized preparation, especially designed for skin testing. The brucellergin test is also performed by injecting 0.1 cc. into the skin of the forearm. A positive reaction by either method is characterized by the development of a circumscribed erythematous, edematous, indurated area at the site of injection. In a positive test, the area of local reaction averages about three-fourths of an inch in diameter, but may vary from one-half inch to three or more inches. The reaction usually reaches its greatest intensity in twenty-four to forty-eight hours; ordinarily it is best to observe the results of the test forty-eight hours after injection. The presence of mild, transient erythema, without edema and induration, is of no significance. In frankly positive cases the induration usually persists for several days. In hypersensitive persons a positive test may be accompanied by a mild, or in some instances a severe, systemic reaction. In such cases the lymphatic channels above the site of inoculation may become red, thickened and painful, and the regional axillary lymph nodes may become enlarged and tender. An exacerbation of symptoms may follow the development of a positive skin test. Focal necrosis at the site of inoculation occurs in a small number of cases.

There is evidence that the injection of heat-killed Brucella for the intradermal test stimulates the production of agglutinins. Evans found that the intracutaneous injection of brucellergin in twelve volunteers caused the development of opsonins in seven and agglutinins in five; in one instance the agglutinins rose from zero to a titer of 1:320. *Hence it is advisable to collect blood specimens for serologic tests before the intradermal test is performed.*

The inadequacies of the agglutination test and the intradermal test, particularly in distinguishing between present and past Brucella infection, led Huddleson, Johnson and Hamann to reintroduce the *opsonocytophagic reaction,* a modification of the Leishman-Veitch technique for determining the phagocytic activity of the blood in the presence of serum opsonins and homologous leukocytes. The opsonocytophagic test is employed in conjunction with the intradermal test or the agglutination test, or both, to determine the immunity status of an individual giving positive tests by either or both methods. The test is performed by mix-

ing 0.1 cc. of the patient's citrated blood with 0.1 cc. of a saline suspension of living Brucella which have been grown for forty-eight hours on liver infusion agar. The suspension should contain at least six billion organisms per cc. of physiologic saline solution (pH 7.0). The mixture is then incubated at 37 C. (98.6 F.) for thirty minutes, after which a small amount of the sedimented cells is removed with a capillary pipette. A smear is then made from a large drop of the cell suspension, dried rapidly and stained with Hasting's stain or Bordet-Gengou's carbol toluidin blue. The number of bacteria in twenty-five polymorphonuclear neutrophilic leukocytes is determined and classified according to the number of bacteria per polymorphonuclear leukocyte; the absence of phagocytosis indicates a negative result; 1 to 20 phagocytized bacteria indicates slight, 21 to 40 moderate, and 41 or more, marked phagocytosis.

According to Huddleson's interpretation, the opsonocytophagic power of the blood is low during the active infective phase of the disease and becomes marked after recovery. On this basis, it is considered that individuals have developed immunity to Brucella if 60 per cent or more of the polymorphonuclear leukocytes show marked phagocytosis. If as many as 40 per cent of the leukocytes show moderate to marked phagocytosis the patient may be infected and has not yet developed any immunity, or he may be uninfected.

While theoretical considerations lend support to the contentions of Huddleson and his associates as to the value of the opsonocytophagic test, it still lacks confirmation. The studies by Calder, and Keller, Pharris and Gaub appear to provide some support to Huddleson's thesis. On the other hand, Evans regards the opsonocytophagic test as the least reliable of the diagnostic tests in cases of chronic brucellosis; she found strongly positive (immune) reactions in four cases from which Brucella were cultivated and weak or moderate reactions in recovered cases. Morales-Otero and Gonzalez tested over 200 individuals (cattle handlers, milkers and laboratory workers exposed to Brucella infection) with a purified Brucella skin-test antigen, agglutination tests, complement fixation tests and opsonocytophagic tests. They found no correlation between cutaneous allergy to Brucella and the opsonocytophagic reaction. Fifteen cases that were positive to the opsonocytophagic reaction gave a negative cutaneous reaction, while eighteen showing a positive cutaneous reaction were completely negative to the opsonocytophagic reaction. Lee Foshay and the writer, working independently, have

found that a significant proportion of patients yield aberrant and unexpected results in relation to their immunity status when the opsonocytophagic test is employed in conjunction with cultural methods, agglutination tests and skin tests. High phagocytic titers (immune reactions) occur in some patients with severe and uninterrupted brucellosis, proved by cultures. Certain recovered patients, asymptomatic for months or years, exhibit marked fluctuations from month to month, running the entire gamut from high to low phagocytosis, or sometimes none at all. *Until more extensive studies have been made on culturally proved cases of brucellosis the results of the opsonocytophagic test should be interpreted with caution and with reservations.*

Hematocytologic studies indicate that leukopenia occurs in the majority of patients with acute brucellosis. In chronic brucellosis, either leukopenia, moderate leukocytosis or normal leukocyte levels may be found. Calder has directed particular attention to the occurrence of active lymphocytogenesis as the most striking and constant feature of the blood picture in all of the manifestations of brucellosis. The lymphocytosis is evidenced by an increase in both percentage values and in absolute numbers of lymphocytes and by an unusually high proportion of immature lymphocytes (lymphocytic shift-to-the-left). Mild anemia of the macrocytic, hyperchromic type is the rule. The erythrocyte sedimentation rate is usually not high, except when complications are present. Calder expresses the belief that this combination of white blood cell and red blood cell abnormalities is distinctive for brucellosis and provides an additional confirmatory diagnostic aid.

A lowered basal metabolic rate, vascular hypotension, gastric hypochlorhydria or achlorhydria are commonly observed in patients with chronic brucellosis.

In the acute form of the disease the manifestations are often sufficiently characteristic to justify a provisional clinical diagnosis of brucellosis. The disease has been recognized most frequently in those areas in which investigators have stimulated their medical colleagues to search for it. Many victims of the disease do not appear dangerously ill and there is often a natural tendency to neglect the taking of a detailed history and the performance of a thorough physical examination.

Just as the diagnosis of brucellosis may be missed by too great reliance on any one or all of the diagnostic tests, so also is there danger that the diagnosis may be made much too freely by unjustified reliance

on a positive skin test. This hazard pertains particularly to the diagnosis of chronic brucellosis.

Prognosis

Fatal outcome is rare, having occurred in about 2 per cent of reported cases. During 1936, 107 deaths from brucellosis were officially recorded in the United States. The importance of the disease is not to be judged by the low mortality rate. The prolonged course and the resulting chronic ill health in a high proportion of cases make the outlook much more serious than the death rate would indicate. Death is usually the result of overwhelming acute infection, terminating fatally during the first few weeks of illness, or it follows a relapse at any stage of the disease due to regional localizations of Brucella in such structures as the meninges, brain, heart valves or lungs.

Treatment

The most important consideration in the control of brucellosis is prophylaxis. The widespread distribution of the infection among cattle renders it difficult to control the infection at its source. Many cows have Bang's disease and eliminate the organisms in large numbers in the milk and vaginal discharges without manifesting symptoms of the disease (abortion, mastitis, sterility and lessened milk yield).

Since 1934, the United States Department of Agriculture has been engaged in a laudable campaign directed toward eradication of brucellosis in cattle. After fifty-five months of diligent effort, ending January 31, 1939, more than a million and a half cattle (approximately 5.5 per cent of the number tested) were found to give positive tests for brucellosis; the infected cattle were condemned and the farmers and dairymen received indemnities to compensate for the loss of the cattle. Unfortunately, no similar campaign has yet been inaugurated to control the disease in hogs and goats.

There is but one logical method for preventing the transmission of milk-borne infection to human beings, and that is by pasteurization. Brucellosis is only one of the formidable list of diseases transmitted to man through the use of raw milk and other unpasteurized dairy products. Murray, McNutt and Purwin, Boak and Carpenter, and Zwick and Wedeman have demonstrated that complete pasteurization (143-145 F.

(61.6-62.7 C.) for thirty minutes) will destroy Brucella. *The need for strict supervision of the pasteurization process is apparent.* For the protection of the health of those persons whose occupations bring them in direct contact with infected animal tissues we must rely upon education and the institution of precautionary measures.

For those persons who live on farms, or in small communities where pasteurization is not yet practiced, home pasteurization may be carried out by placing the milk in an aluminum vessel and heating it to 155 F. (68.3 C.), stirring constantly, then immediately setting the vessel in cold water and continuing the stirring until cool.

The *general management* of the patient with brucellosis will be largely determined by the prevailing symptoms and signs. General therapeutic considerations will vary greatly in individual patients. The therapeutic program for patients with acute brucellosis is quite different from that employed for the chronic form of the disease.

In severe cases of acute brucellosis, the general supplementary management is essentially that employed for any acute febrile disease, characterized by fever, chills and sweats. If the sweating is of a drenching character special provisions should be made for the protection of the mattress and for changes of bed linen and gowns. If the fever exceeds 104 F. (40 C.) tepid sponge baths are indicated; *antipyretic drugs should be avoided.* The patient should remain constantly in bed during the febrile phase and for at least one week after the temperature has returned to the normal level. Skilled nursing care is an essential requirement in the severe cases. The same precautions should be taken as regards the disinfection of urine and feces as in cases of typhoid fever. As the fever abates, a liberal diet of high caloric value is required, particularly for patients who lose considerable weight. The patient should be cautioned against resuming even moderate activity until there has been an appreciable gain in strength. Two or three additional weeks of rest will often save the patient from several months of partial disability.

In cases of chronic brucellosis, the general management must be strictly individualized. Since most of these patients are ambulatory and are at least attempting to perform some work, often at great effort, the program should be directed towards a maximum amount of rest. This may entail a regulation of the hours of work in order to avoid excessive fatigue. Since most of these patients suffer from the symptoms ordinarily ascribed to neurasthenia, a generous amount of practical psycho-

therapy, largely directed towards reassurance, is a fundamental requirement. The members of the patient's family should be fully informed as to the nature of the illness in order to enlist their sympathetic understanding and to avoid their stigmatizing the patient as neurotic or as a malingerer. The common symptoms of headache, backache, joint and muscle pains, insomnia, anorexia, constipation and anemia usually yield to appropriate symptomatic measures.

Specific Therapy

While there is considerable evidence that the employment of various types of serum therapy and vaccine therapy has greatly improved the outlook for most patients suffering from acute or chronic brucellosis, it is extremely difficult to evaluate the effectiveness of any form of specific therapy in a disease characterized by natural remissions and by an extremely variable symptomatology. The reported results of vaccine therapy or serum therapy run the entire gamut from pessimism to hyperenthusiasm. More extensive controlled and systematic studies on a large number of patients, carried out over a period of many years, are necessary before definite statements can be made. It would appear, however, that sufficient data have been accumulated to justify the continued and extended use of some of the specific agents.

A. SERUM THERAPY

Interest in serum therapy, which had waned following the earlier appearance of several unfavorable reports, has been revived by the development of a more potent anti-Brucella serum by Foshay and his associates at the University of Cincinnati. Detoxified Brucella antigens are employed for the development of the antiserums in goats or horses. Several favorable experiences with the Foshay serum have been recorded by other workers. This type of antiserum therapy should be restricted to patients with acute or subacute brucellosis, preferably to those who have had the disease less than eight months. The dosage recommended by Foshay is as follows: For adults suffering from moderately severe to severe manifestations of the disease, the average total dose is 60 cc., given by three daily intravenous or intramuscular injections of 20 cc. each or by two daily injections of 30 cc. each; in unusually severe infections, 90 to 120 cc. may be given in unit doses of 30 cc. during a period of forty-eight to seventy-two hours; for children, a total of 20 to 30 cc.

may be given, either intramuscularly or subcutaneously, in daily doses of 10 cc. each.

Serum therapy is not indicated in cases of chronic brucellosis of more than eight months' duration, unless sudden, severe exacerbations occur. Such abrupt relapses are usually the result of regional localizations involving the meninges, brain, spinal cord, heart valves, lungs, liver, spleen and bone marrow. In such cases, the dosage of serum would be that recommended for unusually severe infections.

Scattered reports of the use of convalescent human serum, blood transfusions from recovered donors, or immunotransfusions from donors who have received prior injections of heat-killed Brucella, have appeared. Even though the number of cases is small and the period of observations not sufficiently long for accurate evaluation, the results were sufficiently gratifying to justify further trials, particularly as regards immunotransfusions.

B. VACCINE THERAPY

It seems probable that the earlier discrepant reports of the effectiveness of vaccine therapy had their basis in a lack of standardized methods for the preparation of the vaccines, both as regards the choice of suitable strains and the concentration of the vaccine. These difficulties appear to have been largely overcome in recent years by the development of better standards for the preparation of therapeutic vaccines.

Brucella melitensis (varieties abortus and suis) vaccine, N.N.R., has been widely employed and is available through the usual trade sources. This vaccine is a saline suspension of heat-killed or formalin-killed Brucella abortus and suis organisms in equal quantities. Vaccines prepared from the melitensis variety of the organism should be utilized only in the treatment of the relatively rare Brucella melitensis infections.

Experience has taught that no rigidly standardized scheme of dosage of vaccine is applicable to patients with brucellosis. Experience and good judgment are essential requisites in determining the proper dosage for each individual. The usual procedure with the commercially available vaccine is first to test for hypersensitiveness by injecting 0.05 cc. of a 1:10 dilution of the vaccine intracutaneously. If the patient does not experience an excessive local or systemic reaction within the next forty-eight hours, an initial therapeutic dose of 0.25 cc. is injected into the deep subcutaneous tissues, or preferably into the muscle. Local reactions are minimized by intramuscular injections. If no untoward reaction fol-

lows the first injection of 0.25 cc., a second dose of 0.25 cc. is given three days later. The dosage is then increased in increments of 0.25 cc., at intervals of three days, until a dosage of 1 cc. is reached. Ordinarily, two injections of 0.5 cc. and two of 0.75 cc. are given before the 1 cc. dosage is attained. Five to eight injections of 1 cc. each may then be given at three-day intervals.

If the patient is highly sensitized, it is wise to begin with intramuscular doses of 0.1 cc., or, in rare instances of extreme sensitization, with doses of 0.1 cc. of a 1:10 to 1:100 dilution of the vaccine, and gradually increase the dosage by 0.1 cc. increments until a dosage of 1 cc. is reached. If, during the course of vaccine injections an unusually severe local or systemic reaction should occur it is desirable to reduce the next dose to one-half the amount which produced the severe reaction and then cautiously and gradually increase the succeeding doses.

A series of four to six or more sharp systemic, febrile reactions, usually accompanied by a transient exacerbation of symptoms, is the goal of the treatment. Hence, only extreme local or general reactions should be avoided. Elevations of temperature to 103-105 F. (39.4-40.6 C.) are not uncommon within four to eight hours after the injection of vaccine. Such systemic responses may occur following the first injection of a small quantity of vaccine or may not occur until relatively large doses are given. In chronic brucellosis larger doses of the vaccine may be required; if no reaction is provoked after five or six 1 cc. injections, the dosage may be gradually increased by 0.5 cc. increments to 2 or 3 cc.

While some patients who have obtained an apparently satisfactory response to vaccine therapy have had little or no thermal reaction, the most prompt and lasting results have occurred in those who have experienced several such reactions.

Erythema and tenderness at the site of vaccination occur commonly for a day or two following injections. In about 5 per cent of cases, a local hard tumefaction may persist for much longer periods. In a small proportion of such cases sterile abscesses or local areas of necrosis have developed.

C. BRUCELLIN THERAPY

Brucellin is a fraction of Brucella cells obtained by growing the organism in liver broth. The bacteria-free active agent is recovered from the liver broth filtrate. This preparation was devised by I. F. Huddleson and may be procured at the Central Brucella Station, Michigan State

College, East Lansing, Michigan.

The dosage of Brucellin must also be adjusted to suit the requirements of individual patients. After the extent of sensitiveness has been determined by the intradermal injection of 0.1 cc. of Brucellin, the usual procedure in non-hypersensitive patients is to give repeated injections of 1 cc. at intervals of three days until the morning and evening temperatures between the intervals of injection tend to become subnormal. Here again, one object of this form of therapy is the production of a series of four or more febrile, systemic reactions. If the duration of illness is less than ten weeks, the likelihood of recovery following four 1 cc. injections is greater than if the duration is longer than ten weeks. Patients with long-continued chronic brucellosis require a larger number of injections and may require gradually increasing amounts up to 5 cc. before satisfactory reactions are produced. In highly sensitized persons, it is advisable to start with intramuscular doses of 0.1 cc. If there is no severe systemic reaction following this injection, each succeeding dose may ordinarily be doubled, until the larger dosage is attained.

In children, the initial dose of Brucella vaccine or Brucellin should not exceed 0.1 cc. and succeeding doses should be increased by not over 0.1 cc. increments. Considerable dilution of the vaccine is required for hypersensitive children.

A partially oxidized detoxified vaccine, devised by Foshay and O'Neil has been used with apparent success. Much smaller doses are given subcutaneously at more frequent intervals. The few reports of results indicate the recovery rate equals that of other vaccines or Brucellin. Local or constitutional reactions do not occur with the oxidized vaccine. It has been recommended chiefly for the treatment of chronic brucellosis.

While it is difficult to evaluate the results of vaccine or Brucellin therapy, the experiences of many investigators indicate that about 60 per cent of patients with brucellosis obtain apparently complete recovery after a satisfactory course of either agent. An additional 25 per cent appear to obtain some benefit, while the remaining 15 per cent are not improved.

The contraindications to vaccine or Brucellin therapy are heart disease, renal disease, arteriosclerosis, meningeal or cerebral localizations of Brucella or the acute fulminating (malignant) form of the disease.

NON-SPECIFIC PROTEIN THERAPY

Injections of foreign protein substances, such as sterile skimmed milk, typhoid vaccine or typhoid-paratyphoid vaccine have been utilized for the production of non-specific shock reactions in the treatment of brucellosis. Erwin and Hunt reported good results in twenty patients with acute and subacute brucellosis following the intravenous injection of killed typhoid-paratyphoid organisms. The usual initial dose was 30 to 50 million killed organisms, with two to six additional injections, increasing the dosage by increments of 25 million organisms.

CHEMOTHERAPY

Neoarsphenamine, mercurochrome, acriflavine, metaphen, thionin, methylene blue, methyl violet, gentian violet and other chemical substances have been used in the treatment of brucellosis. In most instances the reports of the apparently successful use of these substances were based upon observations limited to small numbers of patients. The very length of the list argues against the specificity of any of them.

Sulfanilamide and related compounds have been heralded as effective agents in the treatment of brucellosis since 1936. After the first wave of enthusiasm, usually based on short observations on relatively few patients, other reports of less favorable or entirely negative results have appeared. Blumgart and Gilligan analyzed the results reported in the thirty-one papers which appeared between 1936 and 1939. Twenty-four of the reports were concerned with only one or two patients. Of the seventy-four cases treated with sulfanilamide or allied compounds, there were sixty-eight apparent recoveries and six failures; fourteen of the sixty-eight patients (20 per cent) exhibited relapse after apparent recovery. The daily dosage of sulfanilamide employed in most cases was 4 to 6 gm. (60 to 90 grains) during the period of fever, with gradually diminishing dosages for three or four days after the fever abated. The administration of the drug was rarely continued for more than twelve days. Bynum reported six cases of brucellosis unsuccessfully treated with large doses of sulfanilamide. Long and Bliss report recurrence of infection in four of five patients whose immediate response to sulfanilamide therapy was apparently quite satisfactory; in two instances Brucella was recovered from the blood after sulfanilamide therapy was discontinued. The writer has had similarly disappointing experiences in several cases treated with large doses of sulfanilamide, controlled by

determinations of the sulfanilamide concentration of the blood. *Until more extensive and extended studies are made on culturally proved cases, the value of sulfanilamide therapy in cases of brucellosis must be regarded as undetermined.* In this connection it might be well to recall the fact that a temporary remission is not synonymous with cure.

ARTIFICIAL FEVER THERAPY

The observation that recovery from brucellosis often followed the induction of fever by chemical or biological agents led Prickman and Popp to investigate the possible usefulness of artificial fever induced by physical means in the management of brucellosis. Each of three patients was given three artificial fever treatments, each of five hours' duration, at a rectal temperature of 105-106 F. (40.6-41.1 C.); all were benefited by the treatment. Zeiter described a similarly favorable experience. More recently, Prickman, Bennett and Krusen analyzed the results of treatment with physically induced hyperpyrexia in twenty-one cases of brucellosis; apparent cure resulted in 80.9 per cent of the patients. The duration of the disease prior to artificial fever therapy varied from ten days to two and one-half years. The authors expressed the belief that fever therapy was most efficacious in the acute and subacute febrile stages of the disease. Simpson, who has had similar favorable results, reserves artificial fever therapy for those refractory patients who do not respond to vaccine therapy. Artificial fever therapy should be carried out only in properly equipped institutions by thoroughly qualified physicians and nurse-technicians.

MISCELLANEOUS THERAPY

Since some degree of anemia is a common finding in brucellosis, it should be combated with appropriate dietary, iron or liver therapy. Repeated small transfusions (200 cc.) are of value in the management of the more severe grades of anemia. In the more chronic forms of the disease, in which severe anorexia is a prominent feature, vitamin deficiency is common. Large doses of vitamin B, with reinforcement of vitamin A, C and D intake, have been effective in relieving this distressing symptom.

SUMMARY AND CONCLUSIONS

1. The author's prediction of a decade ago, greeted with some skepticism at that time, that brucellosis would become recognized as a public health problem of major proportions has been fulfilled. Of the

220 cases of brucellosis studied by the author, all but 24 occurred prior to the passage of a universal pasteurization ordinance in 1931. In each of the 24 cases occurring during the past nine years the patient had consumed raw milk elsewhere prior to the onset of illness.

2. The symptomatology of the acute and the chronic forms of brucellosis varies greatly. The diagnostic criteria for acute brucellosis are usually not applicable to the chronic form of the disease. There is little doubt that the chronic ambulatory form of brucellosis is widely prevalent, is often confused with other diseases, and frequently is not recognized. Many "neurasthenics" and patients with so-called "fever of unknown etiology" have been found to be victims of chronic brucellosis. Less than 10 per cent of patients with chronic brucellosis have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis.

3. The only diagnostic procedure by which the diagnosis of brucellosis may be established with certainty is by the cultivation and identification of the organism. The agglutination test and skin test are of considerable value in the diagnosis of acute brucellosis, but these procedures are notoriously inadequate as diagnostic aids in cases of chronic brucellosis. A positive agglutination test, particularly of low titer, and a positive skin test do not indicate that the person is suffering from brucellosis at the time the tests are made. Both the agglutination test and the skin test will yield entirely negative results in an appreciable number of persons from whose blood Brucella may be recovered.

4. In our hands, the opsonocytophagic test has yielded a high proportion of inconsistent results. We have found this test to be of little or no value as a diagnostic procedure or as a guide to therapeutic response.

5. Since it is now well-established that brucellosis is caused most frequently in this region by the ingestion of raw milk containing Brucella, the most important consideration in the control of the disease is adequate, controlled pasteurization of all milk and dairy products.

6. Brucella vaccine therapy has produced favorable results in from 60 to 85 per cent of patients with either acute or chronic brucellosis. Sulfanilamide and other sulfonamide drugs are apparently of little benefit. Artificial fever therapy has yielded favorable results, particularly in those refractory patients who do not respond to vaccine therapy.

DENTAL FOCI OF INFECTION*

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My experience as a pathologist and a teacher of both general and dental pathology influenced the selection of, and limitation of this subject to, "Dental Foci of Infection." What can be said that will be helpful in your evaluation of suspect dental lesions?

The problem of physician, dentist, or both is essentially one of diagnosis. Proper appraisal of the history, physical findings and accessories or aids is the only satisfactory method. Many failures, which should not be failures, result from too much attention to accessories. The history is more or less neglected and the clinical examination slighted. Appreciation of the time factor should be the greatest help and in those cases suspected of dental foci, knowledge of this time element will often be a most valuable link in the diagnostic chain.

The concept of infection seems to have strayed from the narrow path of its original meaning. It depends on the struggle between the invading agent and the defending host.[1] First, the pathogenic organism must exhibit the ability to gain access, survive and multiply; second, it is opposed by the defensive mechanism of the body which includes immunological processes and tissue changes. The latter is the primary concern of a pathologist.

The importance of the oral cavity as a portal of entrance and a breeding place for microörganisms is apparent. When the anatomy and physiology of the teeth, their supporting structures, the gingivae and alveolus are considered, they offer a constant nidus for the entrance and propagation of infection. This was recognized by several investigators. William Hunter,[2, 3, 4] in his "Oral Sepsis as a Cause of Systemic Disease," did much to disseminate this idea.

The overemphasis of laboratory aids or accessories, to the neglect of history and clinical findings, calls for comparison and evaluation, especially for bacteriology and x-ray.

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Bacteriology

The literature on bacteriological investigation of dental foci of infection concerns three groups of bacteria. The first includes the fusiform bacilli and spirochetes or Vincent's organisms. Although there is increasing evidence that fusospirochetosis may cause systemic disease,[5, 6] the other two groups are of more concern now. The second contains mainly the B. acidophilus group. Though the etiology of caries is not fully understood, there are two schools of thought. One emphasizes the internal mechanism and nutrition of the tooth, and the other advocates the external or bacteriological and chemical processes. By the fermentation of carbohydrates, these organisms produce organic acids and enzymes active in cavity formation. The dissolution of enamel and dentine or cement leads to involvement of the pulp, and a direct circulatory route for the entrance of bacteria through the apical foramen. This is the portal of entry for the third group, in which the chief offender is the Streptococcus viridans.

Demonstration of Bacteria

Bacteria have been demonstrated in many ways and in various sites. Smears, cultures, and animal inoculation have been used to isolate and identify organisms. Tissue stains have aided in both biopsy and postmortem material. Periapical tissues, pyorrheic pockets, saliva, carious enamel and dentine, pulp, pulp stones and periapical bone have yielded various positive findings. Microörganisms have been found in blood, joints, heart, kidney, gastrointestinal tract, muscle, prostate, eye, nose, throat, bone, feces and urine which were considered to have their origin from dental foci. However, bacteria can be active long before they produce histopathological tissue changes or x-ray evidence of their presence.

Blood Cultures

Recent investigations can be presented succinctly in two groups:

I. Occasionally positive blood cultures have been demonstrated in healthy individuals;[7] temporary or transient bacteriemias have been reported following operative procedures, dressing manipulations,[8] urethral operations[9] and tonsillectomies.[10, 11] In 5,310 blood cultures on hospital cases Fox and Forrester[12] obtained their greatest percentage of

positives in subacute bacterial endocarditis (238 positive cultures).

II. Immediately after extraction, positive blood cultures occur when previously the blood has been negative, and when in a relatively short time, the blood again becomes negative.[13] With periodontal disease the incidence of positive blood cultures after extraction may be even higher.[14, 15] Rocking of teeth or massaging of the gingiva has been followed by positive bacteriemia.[15, 16] Mastication of hard candy has been followed by temporary bacteriemia.[17] Serratia marcesens have been recovered from the blood following extraction, having been thus introduced into the gums.[18]

The phenomenon, anachoresis, whereby certain foreign blood-borne substances, including bacteria, are attracted to and fixed in inflammatory areas, has a direct application to infected teeth. Csernyei's experiments[19] indicate that chronic periapical inflammations have an anachoric effect on microörganisms, and that organisms do not remain in the blood, but take refuge in the area of inflammation. H. B. G. Robinson and L. R. Boling[20] present the results of their experiments in which they were able to produce injury to the pulps of animals, following which they injected certain bacteria into the vein of a hind leg and later definitely recovered organisms from the site of injury.

It has been demonstrated that bacteriemias (determined by positive blood cultures) may be transient, and in many instances be produced by artificial means or in extremely unusual circumstances. Isolation of a bacterium from the blood stream gives neither its origin, nor tells what relation it has to systemic disease already present. In practically all cases of subacute bacterial endocarditis, we incriminate the Streptococcus viridans. In hospitals where repeated positive blood cultures have yielded a Streptococcus viridans, the patient ultimately proves to have either clinically, or at autopsy, endocarditis lenta. Bacteriological evidences as to the type of organism about the tooth and supporting structures favor the green producing streptococcus. However, is it not presumptuous to assume in most of these cases that the organism in the tooth, then in the blood and finally on the heart valve is necessarily the cause?

Finally, it is pertinent to evaluate bacteriological technique and reports. Good technique is extremely difficult, time consuming and expensive. Most of the work, to date, has been with aerobes. Negative results do not always mean that organisms are not present, nor do positive findings always mean that such organisms are causal. Special tests for viru-

lence and specificity, except in the hands of a few experienced workers, are rarely performed and need careful evaluation.

X-RAY

X-ray examinations, when devoid of clinical data, should be regarded only as diagnostic aids or accessories. Compared with the knowledge of the presence of bacteria from a suspicious area, positive x-ray findings are more valuable. Assuming good standard technique, comparisons are based on radiolucent and radiopaque changes. Pathological changes may be present, and even good x-rays show nothing. On the other hand, the size of an x-ray area is not necessarily an index of the activity of a process. When changes are present in hard tissues, i.e., enamel, dentine and cement (the tooth proper) or the bone (the alveolus), the x-ray will be of greater aid than when changes are found in the soft tissue, where, however, sometimes by inference, conclusions may be justified.

As an index of dental infection, a radiolucent area is more indicative of activity than a radiopaque area. Changes have occurred to bring about a decrease in the harder tissue, a removal of the calcium. The most important cause of a radiolucent area is usually destruction, as: (1) In caries due to actual loss of tooth substance; (2) when a root of a tooth has been removed, destroyed or resorbed; and (3) in bone with an abscess; granuloma or cyst; with sequestration in osteomyelitis; with a destructive tumor. Whether the infection is active or latent, and how little or how much it is contributing to a systemic infection is the main question. A single x-ray of a radiolucent area may be difficult or impossible to interpret. When however, successive x-rays reveal further progress and extension, associated with a history and clinical signs and symptoms suggesting a focus of infection, such evidence is strongly convincing.

In the light of infection radiopaque areas deserve less consideration. Increased density or condensation can be illustrated by: (1) enamel nodules; (2) metallic fragments; (3) hypercementosis; (4) productive lesions, as osteogenesis, osteosis (exostosis), osteoma. As a result of infection, radiopaque areas do occur but in general they are best interpreted as bone scars and are testimony to the fact that healing has been adequate.

When successive x-rays originally reveal a radiolucent area, and

subsequently a change to more and more radiopacity, with a history and clinical symptoms and signs suggesting a dental focus, such evidence is quite convincing that the probability of such a lesion causing systemic manifestations is less and less.

Other Tests

The sedimentation test in dentistry, particularly with the present problem has received more attention of late.[21, 22] It is a laboratory aid or accessory which only exceptionally may indicate the activity of a dental focal infection. When a series of successive tests are made for comparison, the information is much more valuable than with a single test, especially in interpretation of the progress of a condition.

In dental literature an increasing number of claims for short wave diathermy have been made. They are no doubt, a direct reflection of the popularity of this procedure in medicine.

Benefits have been claimed not only from a therapeutic standpoint, but even as an aid in the diagnosis of dental infections—"Provocative irradiation."[23]

Several have claimed that the application of "Short Wave" to a suspect dental focus, if active, will be followed by an increase in the sedimentation rate and that this test has considerable diagnostic value.[24, 25]

To elicit information on the vitality of a tooth, pulp testing is valuable. While instruments may be employed for this, there are various clinical methods which are adequate in most cases.

Dental Focal Infection

The crux of this situation is intimately related to a number of conditions frequent in dental practice. It is to be regretted that in many of our medical schools they receive little or no attention. Space will not permit as much consideration as they deserve. Some of the more important conditions are briefly discussed.

Caries, i.e., dental decay is the major problem of dentistry. From such cavities, leading directly to pulp involvement, it may readily be appreciated how bacteria and infection can gain entrance (the most frequent pathway of entrance) to the pulp and the systemic circulation. When evidences of infection are open, i.e., in direct communication with the outside world, drainage is more easily established and the dangers of systemic or distant involvement are less. The lamina dura

when intact, indicates to many the absence of periapical infection.

Periodontoclasia (pyorrhea) represents another major problem in dentistry. Many papers have been written on "pyorrhea" as a probable dental focus and this thought cannot be dismissed lightly. Three possibilities as to the modus operandi should be mentioned: Absorption of bacteria or their products directly into the systemic circulation from pockets; an exudation of purulent or infected material into the mouth and subsequent swallowing of such infected material; lastly, interference with mastication as the result of loose teeth. While the positive proof in support of any of these contentions is difficult, appreciation of the fact that most of the lesions in this condition are open lesions, at least diminishes the probability of absorption of bacteria or their products directly into the systemic circulation. This was one of the main contentions of William Hunter.[2]

In pyorrhea, the chief pathological features are: alveolar resorption, pocket formation, loosening of the teeth with or without suppuration. Usually, calculus and evidences of infection in pockets are present.

Retained Roots. Many statements concerning the danger of such roots are found. The cause of the root retention necessarily influences its danger. Information from the history, as to the probable cause and especially a knowledge of the length of time such retention has been present will be very helpful in evaluating such a focus. Where roots have been retained for years and the x-ray is negative or possibly shows condensation in contrast to a radiolucent area, less consideration as to the probability of an active focus of infection seems justified.

Dead Tooth. When a tooth is traumatized severely so as to completely sever its periodontal attachment with obvious resultant death of the pulp (some reserve the term dead tooth for such a condition) this may or may not act as a dental focus. Usually, such injury will result in loss of the tooth within a short time after the accident. In such cases on account of open socket and free drainage if infection does occur the local defense will usually be adequate. In some cases, however, certain changes may usually be expected, resulting in resorption of the root and eventual loss of the tooth.

It cannot be denied that inadequate or unsatisfactory root canal therapy, sometimes the fault of the dentist, often the neglect of the patient, may be responsible for dental foci. As a result of recent encouraging advances especially in root canal therapy in prevention, diag-

nosis and treatment,[26, 27, 28, 29, 30, 31] we are of the opinion that all pulpless teeth should not be needlessly sacrificed on the altar of focal infection.

Radicular–Granuloma–Cyst. The next group is also frequent and important. As a rule they appear as more or less well localized radiolucent areas as a result of destruction. Their infectious nature cannot be denied. They are practically all associated with, or due to, devitalized teeth, sometimes a tooth which has had root canal therapy, but more often has not.

They are, in contrast to some of the others we have shown, closed lesions; they represent infection, possibly of a latent type, and are thereby a menace.

The more localized, the less the danger; but neither can it be denied that they are very frequently present without active local clinical evidences and in many individuals whose apparent health is excellent, and who remain so indefinitely.

Pulp stones are not uncommonly found in one or more vital teeth. While it is claimed they are of infectious origin,[32] dental foci, or frequently the cause of neuralgia, the evidence appears more against than in favor. Dr. S. Sorrin, one of my associates on the Dental Service at Montefiore Hospital, advises me that in the dental examination of 200 cases of arthritis of various types (composed for the most part of cases of infectious arthritis) he found: 100 were edentulous; 53 had less than 20 teeth and 47 had 20 teeth or more. In these 47, isolated pulp stones (4 teeth or less) were present in 15 patients.

While pulp stones may be composed of dentine or calcium, based upon an understanding of pathological changes in such conditions they are interpreted as degenerative rather than inflammatory.[33]

Periosteal condensation, osteosis and osteoma. It is not always easy to decide whether these changes are dystrophic, neoplastic or inflammatory. As said previously, in general, when of inflammatory or infectious origin, we interpret them as bone scarring and believe they represent evidence of a successful or adequate local defense.

Secondary Manifestations

An extensive list of conditions has been attributed to dental foci. The organs involved include: joints, muscle, nerves, kidney, heart, eye, gastrointestinal tract, nasopharynx and gall bladder. From this list there are three upon which to comment:

I. The possible or probable relation of dental infection to heart disease is so extensive that comment will be made only on the relation of extractions to endocarditis. Recently, several reports [34, 35] on subacute bacterial endocarditis developing within a short time after extraction of (infected) teeth have appeared. In a personal communication, I. Salman, Oral Surgeon and S. P. Schwartz, Cardiologist, of Montefiore Hospital reviewed 215 hospital cardiac cases of rheumatic, arteriosclerotic and syphilitic patients from whom a total of 1126 teeth had been extracted under local anesthesia. No cases of subacute bacterial endocarditis followed.

II, III. Nasopharynx and Eye: More direct mechanisms and pathways of extension have been emphasized by several authors in affections of the antrum[36] and eye.[37] In striking contrast to the other parts of the body, the pathogenesis strongly indicates a direct extension or direct pressure on dental nerves rather than the usually accepted explanation of hematogenous spread.

By better medico-dental coöperation (and lately there have been encouraging evidences of it), greater progress can be made in the prevention, diagnosis and treatment of dental foci of infection. Sometimes, however, it is well to remember that although the ravages of infection may be incapable of repair, the progress of infection may be arrested and the source eradicated; if such cases cannot be improved, at least they should not be left otherwise.

Finally, lest I be misunderstood in my attitude toward bacteriology, let me paraphrase the words of Brutus, It is not that I love Bacteriology less but Pathology more.*

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LYMPHOGRANULOMA VENEREUM*

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LYMPHOGRANULOMA venereum is a widespread, contagious, venereal disease of human beings caused by a minute organism. The infective agent enters the body through the skin of the external genitalia without, however, always producing a demonstrable lesion at the portal of entry. It may also enter by way of the mucosa of the anal or rectal canals, and, much less frequently, by extragenital routes. The virus multiplies readily in the lymph nodes draining the affected areas, and probably, also, in the anal and rectal mucosae. It is transmissible to certain laboratory animals. The lesions of lymphogranuloma venereum are inflammatory in nature, subacute or chronic in quality of reaction, and are often marked by the development of multiple small foci of suppuration. Mortality is low. The disease is systemic with local manifestations appearing chiefly in the anorectal, inguinal and genital regions. It is customary, and convenient, to speak of the disease pictures in these areas as the anorectal, inguinal and genital varieties of lymphogranuloma venereum. There is, however, no evidence of the existence of any difference, other than regional, between the disease in the various sites.

Diagnosis of lymphogranuloma venereum is made, at present, by means of a skin test of a high degree of specificity and sensitivity which has been named after its discoverer, Wilhelm Frei.[1] Treatment of the disease with certain members of the sulfonamide series of drugs, notably sulfanilamide and sulfathiazole, has been very successful. The use of these drugs in the treatment of lymphogranuloma venereum has been of the highest value in that, prior to their introduction, there was no adequate remedy for the disease.

HISTORY

The inguinal variety of lymphogranuloma was the first of the manifestations of this disease to be suspected of being a separate clinical

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entity. John Hunter[2] described, in 1786, a condition in which buboes developed without apparent cause, and were unaffected by mercury. Credit, however, for the earliest definite description belongs to William Wallace[3] who, under the title of "indolent primary syphilitic bubo," gave an accurate description of what would now be regarded as a chronic suppurative case of the inguinal variety of the disease.

H. G. Klotz[4] first called attention to the disease in this country. He reported having seen, in New York City, between the years 1879 and 1889, over 120 cases of a clinical entity which can hardly have been other than the inguinal variety of lymphogranuloma.

Durand, Nicolas and Favre,[5] in 1913, gave the best clinical and pathological study hitherto published of the inguinal disease. They believed, erroneously, that the histological picture of lymphogranuloma resembled that of Hodgkin's disease, or lymphogranulomatosis, and proposed the term lymphogranuloma inguinale for the disease. The clinical and pathological manifestations of lymphogranuloma, however, are not peculiar to the disease and accurate identification was not possible until the introduction of the Frei test in 1925. Study and knowledge of the disease have progressed rapidly following Frei's important discovery.

In 1928, using the recently developed skin test, Frei and Koppel[6] showed that a positive reaction was given by persons presenting inflammatory stricture of the rectum. Experimental proof of the lymphogranulomatous etiology of this condition was established in 1932 by Ravaut, Levaditi, Lambling and Cachera[7] and Laederich, Levaditi, Mamou and Beauchesne[8] who isolated a strain of the virus of lymphogranuloma venereum from inflamed rectal tissue. Mocquot, Levaditi and Reinié,[9] in 1935, isolated from an inflammatory condition of the colon a strain of the virus with which Levaditi, Mollaret and Reinié,[10] in the same year, produced the pathological changes characteristic of lymphogranuloma in the rectum of chimpanzees by direct inoculation into the mucosa.

The etiological agent of lymphogranuloma venereum was shown to be a virus in 1930 by Hellerström and Wassén[11] who inoculated *Macacus rhesus* and *Macacus cynomolgus* monkeys intracerebrally with suspensions of infected human lymph node. Two years later, Levaditi, Ravaut and Schoen[12] reported the transmission of the disease to mice by the intracerebral route. The mouse has since proved to be a very valuable animal in the study of lymphogranuloma. Strains of the virus have

TABLE I

NEW CASES OF LYMPHOGRANULOMA VENEREUM AND TOTAL NEW IN- AND OUT-PATIENT ADMISSIONS, NEW YORK HOSPITAL, 1934-40

Year	No. of new cases of L.V.	Total No. of new admissions	Cases of L.V. per 10,000 admissions
1934	26	43419	6.0
1935	23	44123	5.2
1936	31	45977	6.7
1937	35	44484	7.9
1938	35	43411	8.1
1939	28	41895	6.7
1940 (9 months)	34	31447	10.8

been maintained by successive mouse passage over a period of years and the infected brain has provided useful material, both as a source of virus for experimental purposes and for the performance of the Frei test. The etiological agent of lymphogranuloma was undoubtedly first seen by Gay Prieto[13] in 1927 in the form of small cytoplasmic granules in material obtained from infected inguinal nodes. The granules were one micron or less in diameter and appeared frequently in small aggregations. They were also described, and figured, by Findlay[14] who suggested the possibility that they represented the virus. Granules, however, appear sparsely in preparations of animal and human tissue, a fact which made it impossible until recently to procure active suspensions of the virus free from a large proportion of inert material. The work of Rake[15] and his colleagues, who employed the yolk-sac technique of Cox,[16] has now afforded a means of obtaining rich suspensions of granules. Successive passage of lymphogranulomatous material in tissue culture was observed by Sanders[17] to increase the potency of the virus as high as one thousand times.

STATISTICS OF THE FREQUENCY OF OCCURRENCE OF LYMPHOGRANULOMA VENEREUM

Lymphogranuloma has been studied at the New York Hospital for the past eight years, for most of the time in a clinic specially devoted to

TABLE II

DISTRIBUTION, BY VARIETIES, OF 242 CLINICAL MANIFESTATIONS OF LYMPHOGRANULOMA VENEREUM IN 218 INDIVIDUALS

Variety	No. of manifestations	Per cent
Anorectal	145	59.9
Inguinal	60	24.8
Genital	28	11.7
Asymptomatic	6	2.5
Miscellaneous*	3	1.1

* Includes one case each of carcinoma of rectum, cystitis, and granulomatous pelvic masses.

the purpose. Close coöperation with all of the departments of the hospital has enabled every case of the disease found in the institution to be examined and treated. Table I shows the number of new cases seen annually since 1934, as well as the ratio of these cases to the total annual in- and out-patient new admissions. It will be seen that the proportion of cases of lymphogranuloma is increasing in the community from which the New York Hospital draws its clientèle. A further analysis of the material has revealed the increase to occur equally among all the varieties of the disease.

The local manifestations of lymphogranuloma constitute the most striking element in the clinical picture and occur, in order of frequency, in the anorectal, inguinal and genital regions. Table II shows that the anorectal is approximately two and one half times as common as the inguinal and about five times as frequent as the genital variety. The most frequently occurring combinations of varieties are the genital and inguinal and, less commonly, the anorectal and inguinal.

A small proportion of individuals give positive Frei reactions without any evidence of an existing, or preceding, infection with lymphogranuloma. Such people are usually detected in the performance of surveys of the incidence of the disease in a community, or during investigation of the contacts of an infected person.

Clinical manifestations of the disease, which do not fall into one of the three main varieties, represent about one per cent of the cases and,

in our material, are composed of, respectively, carcinoma of the rectum, cystitis, and granulomatous pelvic masses.

The Anorectal Variety of Lymphogranuloma Venereum

In conformity with all of the manifestations of the disease, the anorectal variety is acquired chiefly by sexual contact. Evidence which has been presented elsewhere, by the author and Henry,[18] has shown that most cases of this variety, in males, arise by the direct implantation of the virus upon the anal or rectal mucosae, through the practice of sodomy. Infection of the lower bowel has also been acquired, in adults and in children of both sexes, by the use of an enema tip in common with a person suffering from the anorectal variety of the disease. It is clear, therefore, that the mucosa of the lowest portion of the human bowel provides an excellent medium for the growth of the virus of lymphogranuloma venereum. Experimental evidence has shown this to be true for the chimpanzee.[10] The mode of acquisition of the anorectal disease by women has been the subject of much discussion. One school, represented by Bensaude and Lambling[19] in France, is of the opinion that owing to the intimate connection between the vaginal and perirectal tissues, the disease begins in the latter tissues and spreads through the rectal wall into the mucosa. In support, it was claimed that of eighty women with rectal stricture, only twelve showed accompanying active inflammation of the rectal mucosa. These authors said, in effect, that if a case of anorectal lymphogranuloma showed stricture and proctitis, it could be assumed that the disease began in the rectal mucosa. If, however, there were stricture alone, the condition probably began outside the rectal wall and traveled through to the mucosa.

Examination of our material on this subject reveals that of sixty-seven women with stricture, no less than sixty-two, or 92.5 per cent, had an accompanying proctitis. By Bensaude and Lambling's own criterion, therefore, practically all anorectal infection with lymphogranuloma in women begins upon the mucosal surface and not outside the bowel wall. I am of the opinion that, in women, the virus, deposited during the sexual act by the infected partner, is enabled through the moisture of the parts to find its way to the anorectal mucosa and there to flourish, as in the case of the male. I am prepared to concede to Bensaude and Lambling the existence of some cases of anorectal lymphogranuloma which begin in the outer coat of the bowel. The clinical

TABLE III

ANALYSIS OF 145 CLINICAL MANIFESTATIONS OF THE ANORECTAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	Number	Per Cent
Stricture with proctitis	107	73.8
Stricture without proctitis	7	4.8
Proctitis without stricture	14	9.7
Esthiomène with stricture and proctitis	3	2.0
Fistula-in-ano	8	5.4
Perirectal abscess	2	1.4
Scarring of perianal tissues	1	0.7
Rectovaginal fistula	1	0.7
Elephantiasis of female genitalia with stricture	1	0.7
Elephantiasis of male genitalia with stricture and proctitis	1	0.7

TABLE IV

RACE AND SEX DISTRIBUTION OF 128 CASES OF THE ANORECTAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	Total cases	Per cent			
		White male	White female	Black male	Black female
Stricture with proctitis	107	38.3	15.0	3.7	43.0
Stricture without proctitis	7	28.6	14.3	0.0	57.1
Proctitis without stricture	14	71.4	7.1	21.5	0.0

condition in such cases is probably stricture without proctitis, of which we have only seen seven cases, two in men and five in women.

The clinical manifestations which are included in the anorectal variety of lymphogranuloma are chiefly the three entities of stricture with proctitis, stricture without proctitis and proctitis without stricture. These comprise over 88 per cent of the variety. The frequency of their distribution by race and sex is shown in Table IV where the comparatively high proportion of cases in white males should be noted.

I believe that proctitis without stricture represents the earliest objective sign of anorectal lymphogranuloma, and that, untreated, the great majority of such cases proceed to the development of stricture while the proctitis is still active. Of fourteen cases of proctitis without stricture I have only observed one to heal spontaneously, and that in a white man. Thirteen of the fourteen individuals were male homosexuals who adopted the passive role. Consideration of the history of their infection indicated that an average period of six weeks elapsed between infection of the rectal mucosa and the development of symptoms.

It should be the endeavor of all persons interested in the study of lymphogranuloma venereum to detect cases of the anorectal variety in the "proctitis without stricture" stage. Complete and rapid cure can then be obtained in over 75 per cent of cases. It is more difficult to heal a proctitis after the development of stricture. Little more than one-tenth of our cases of proctitis were observed before stricture had developed.

The earliest symptom of proctitis is the passage of blood and pus per anum. This is a direct consequence of the replacement of a portion of the anorectal mucosa by granulation tissue. Untreated, the granulomatous process extends deeper into the bowel wall, beginning usually at the posterior aspect and ultimately encircles the lumen. In the majority of cases, the replacement of granulation tissue by fibrous tissue begins to be evident, as a narrowing of the anal or rectal canals, less than three months after the onset of proctitis. In untreated cases, narrowing is slowly progressive.

I have only been able to observe closely three untreated persons during progression from early infection to complete closure of the bowel. In two of these the gamut of the disease was run in six, and in the third, in seven years. The number of cases, however, in which colostomy is required for relief of obstruction is relatively few, only nineteen persons out of a total of 128, or 14.8 per cent, having had to submit to this operation.

A question may be raised at this point as to the proportion of cases of stricture with proctitis, stricture without proctitis and proctitis without stricture which are lymphogranulomatous in origin. The question is answered in Table V in which it is assumed that clinical conditions may be regarded as lymphogranulomatous when the Frei reaction is positive, and non-lymphogranulomatous when it is negative. Accordingly,

TABLE V

THE FREI REACTION IN CERTAIN CLINICAL CONDITIONS

Clinical condition	Number of Cases			Per cent Frei-positive
	Frei-positive	Frei-negative	Total	
Stricture with proctitis	107	3	110	97.3
Stricture without proctitis	7	3	10	70.0
Proctitis without stricture	14	8	22	63.6
Fistula-in-ano	8	17	25	32.0
Perirectal abscess	2	8	10	20.0
Ulcerative colitis	0	29	29	0.0
Regional ileitis	0	3	3	0.0

97 per cent of cases of stricture with proctitis, 70 per cent of cases of stricture without proctitis and 63 per cent of cases of proctitis without stricture are due to the virus of lymphogranuloma.

In view of the readiness with which the virus produces lesions in the lower bowel, our material was further studied to determine the extent to which the Frei reaction is positive in acute and chronic ulcerative colitis and in regional ileitis. No positive reaction was obtained in twenty-nine persons with ulcerative colitis or in three with regional ileitis. It may, therefore, be assumed that the virus of lymphogranuloma venereum does not often play a demonstrable part in the etiology of these two conditions. Our results with ulcerative colitis are in keeping with the experience of Rodaniche, Kirsner and Palmer[20] who reported that thirty-two of thirty-four patients with chronic ulcerative colitis had negative Frei reactions and showed no evidence of neutralizing antibodies in their sera against the virus of lymphogranuloma venereum. In regard to the two Frei-positive persons in their series, consideration was given to the possibility that the virus, although not directly responsible for the bowel ulceration, might have paved the way for other necrotizing agents to become established, as Frei originally suggested.

The remaining clinical manifestations of the anorectal variety of lymphogranuloma are shown in Table III. With the possible exception of esthiomène, which can be closely mimicked by granuloma venereum

TABLE VI

CLINICAL MANIFESTATIONS OF 60 CASES OF THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	No. of cases	Per cent
Suppurative adenitis, unilateral	34	56.7
Suppurative adenitis, bilateral	9	15.0
Non-suppurative adenitis, unilateral	14	23.3
Non-suppurative adenitis, bilateral	3	5.0

and which may occur without rectal involvement, the seven lowest entities in the table are by no means strictly of lymphogranulomatous origin. Further consideration of Table V shows that only about one-third of the cases of fistula-in-ano, and approximately one-fifth of those of perirectal abscess, are due to the virus of lymphogranuloma.

A word should be said about esthiomène, a term which, in the original Greek, meant eating or eroding. The disease is peculiar to women and the original description given by Huguier[21] in 1849 is applicable today. He said, "This chronic malady is characterized by a leaden or violaceous tint of the parts. Deformity, ulceration and destruction may occur with concomitant hypertrophy and infiltration of such a nature that the orifices and canals which open into the vulvoanal region can be at the same time ulcerated, enlarged and strictured."

THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

The inguinal variety results from the deposition of the virus within the territory drained by the inguinal and femoral nodes. The actual site of invasion of the tissue—the primary lesion—is not often demonstrable. In sixty cases of this variety in our material, it was present in fourteen, or 23.3 per cent.

The virus is lymphotropic and produces clinical manifestations in the affected nodes 7 to 21 days after the infecting coitus. The nodes enlarge, sometimes to a considerable size, are painful, and the overlying skin is of a dusky red or purplish tint. In Table VI are shown the clinical manifestations of the inguinal variety in our material. In about four-fifths of the cases the disease is unilateral and in the remaining one-fifth,

TABLE VII

RACE AND SEX DISTRIBUTION OF 60 CASES OF THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Race and Sex	No. of cases	Per cent
White male	39	65.0
White female	2	3.3
Black male	15	25.0
Black female	4	6.7

bilateral. Frank pus appears in the nodes in approximately three-quarters of the infected persons and, in the absence of treatment, breaks through the overlying skin. The sinus thus formed may persist for months constantly draining seropurulent material. Many of the non-suppurative cases heal spontaneously.

The most striking element in the architecture of the diseased node is the presence of a large number of small foci of suppuration which are termed stellate abscesses.

The inguinal variety of lymphogranuloma venereum occurs rarely in women. In our series of sixty cases only six, or 10 per cent, were found in women (Table VII).

The Genital Variety of Lymphogranuloma Venereum

Table VIII shows the frequency of occurrence in our material of the entities which comprise this condition. Primary lesions constituted 50 per cent of the genital manifestations. Satellite adenopathy was not always a concomitant of the primary lesion nor was such adenopathy always purulent. The common type of primary lesion is an oval vesicle on a slightly larger, non-indurated, erythematous base. It measures in the neighborhood of 6 millimeters in the longer diameter which is usually placed at right angles to the long axis of the penis. It does not produce subjective symptoms and is commonly found on the shaft or glans near the coronal sulcus. Primary lesions of the vesicular type generally disappear within 2 weeks without leaving a trace of their presence. Ulcerated primary lesions occur rarely, and when they do a concomitant chancroidal or syphilitic infection is sometimes found. Primary le-

TABLE VIII

CLINICAL MANIFESTATIONS OF 28 CASES OF THE GENITAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	No. of cases	Per cent
Primary lesion with adenitis	10	35.7
Primary lesion without adenitis	4	14.3
Esthiomène with and without rectal involvement	6	21.4
Elephantiasis of penis	5	17.8
Elephantiasis of labium majus	1	3.6
Abscess of vaginal wall	1	3.6
Periurethral abscess	1	3.6

sions of lymphogranuloma are infrequent in women, two only having been observed in our material, one on the labium majus and the other on a perianal tab.

Esthiomène is the second in order of frequency of the genital lesions and has already been described. Elephantiasis of the male and female genitalia produced by the virus is indistinguishable clinically from that due to any of the other known causes of the condition. Elephantiasis of the penis may be produced by the lymphogranulomatous process itself or may follow extirpation of bilaterally involved nodes. Of five cases in our series, three were the sequel of radical surgery and two arose spontaneously.

PARINAUD'S CONJUNCTIVITIS

Curth[22] recently reported the case of an individual who developed, in May 1932, a painless conjunctivitis of the right eye following perverted intercourse. The right preauricular and submaxillary nodes became swollen and tender. Treatment with ineffectual remedies was continued until 1933 when vision was lost in the affected eye. The condition was untreated for the next 5 years during which there was slow progression of the lesion. In November 1938, the right eye showed swelling and inflammation of both lids with considerable edema, especially of the lower lid, and some purulent conjunctival discharge. There was marked destruction of the inner surface of the lids. The right globe

TABLE IX

CLINICAL CONDITION OF 11 PERSONS FROM WHOM SEMEN WAS OBTAINED FOR TESTING FOR LYMPHOGRANULOMA VENEREUM

Case	Nature and duration of clinical condition
1	Active proctitis, 13 months
2	Active proctitis, 3¼ years
3	Active proctitis, 4 years
4	Active proctitis, 4½ years
5	Active proctitis, 6 years
6	Unhealed suppurative groin nodes, 10 days
7	Healing non-suppurative groin nodes, 3 weeks
8	Suppurative groin nodes, healed, 4 weeks
9	Suppurative groin nodes, healed, 16 months
10	Suppurative groin nodes, healed, 22 months
11	Unhealed primary penile lesion, 14 days

was intensely injected. The cornea was opaque. There was no longer enlargement of any of the lymph nodes. Experimental work by Curth and his colleagues established the lymphogranulomatous etiology of the conjunctivitis, thereby confirming the original observation of Levaditi, Bollack, Basch and Desvignes,[23] in 1936.

Asymptomatic Cases of Lymphogranuloma Venereum

This group comprised three white men and three white women in all of whom there was neither existing evidence, nor past history, of infection with the virus. All, however, gave a positive Frei reaction. The marital partners of two men and one woman presented active lesions in the inguinal nodes, the anorectal mucosa and bladder wall respectively. Examination of the contacts of the other three persons was not possible.

Consideration of the group of asymptomatic cases leads to the question as to whether reservoirs of the virus exist other than in the discharges from the bowel and from the infected nodes. An attempt was made by the author to answer this query in 1935 by the examination of specimens of semen from eleven individuals who presented active or healed manifestations of lymphogranuloma. The nature of the lesions

which were presented by the group is shown in Table IX. The existence of virus in the semen was sought by diluting the material with an equal volume of physiologic saline, inactivating by heat, as in the preparation of Frei antigen, and injecting 0.1 cc. intradermally into lymphogranulomatous subjects. In the presence of inactivated virus, positive Frei reactions would have followed this procedure. In no instance, however, was such a reaction obtained. It was therefore concluded that the virus of lymphogranuloma venereum is not present in measurable quantity in the semen and that infection is probably not transmitted by this secretion. The apparent lack of infectivity of semen suggests that lymphogranulomatous proctitis following sodomy arises from an open primary lesion in the active partner, or from an infection of his bladder mucosa.

The Systemic Manifestations of Lymphogranuloma Venereum

The chief systemic manifestation of lymphogranuloma venereum is the hypersensitivity of the skin as a whole to the intradermal injection of suspensions of the inactivated virus. In the case of the inguinal variety of the disease, this develops at about the same time as the enlargement of the nodes and, in the anorectal variety, approximately one month after the appearance of the anal discharge.

Lymphogranuloma venereum may present a clinical picture of acute or chronic febrile illness in which local manifestations are present only in minor degree or may be entirely absent. Harrop[24] and his colleagues have recently reported such cases in workers in the virus, two of whom apparently acquired the infection through the respiratory passages. In one instance the sole localizing manifestation was a moderately enlarged supraclavicular node. In the other there were a greatly swollen uvula, non-suppurative cervical adenitis and recurrent bouts of pyrexia of moderate degree. A third person showed only malaise, fleeting muscular pains, and mild fever.

The inguinal variety of lymphogranuloma is usually ushered in with fever of short duration. Chills and joint pains may be present. The patient is seldom more than mildly ill.

Constitutional manifestations rarely accompany the onset of the anorectal variety. As the disease progresses, however, the individual presents the picture of chronic illness. Loss of weight appears most commonly and is accompanied by anorexia, insomnia and nervousness.

Symptoms of intestinal obstruction are much less frequent than the narrowing of the rectal lumen would lead one to expect. After the disease has persisted for several years, arthritis develops in about 10 per cent of the cases. The joints most commonly affected in our series were the wrists, fingers, elbows, ankles and knees in descending order of frequency. There is hydrops of the affected joint and erythema of the overlying skin. Aspirated synovial fluid is bacteriologically sterile and does not contain the virus. Joint destruction does not occur and full function is ultimately restored. Untreated arthritis waxes and wanes over a period of years and is sometimes of sufficient severity to require bed rest.

A systemic effect of lymphogranuloma reported by Gutman[25] is hyperproteinemia due to a large increase in serum globulin. It was found that, of seventy-two lymphogranulomatous persons in all stages of the disease, two-thirds had total serum proteins in excess of 8.0 per cent, the upper limit of normal; and approximately four-fifths had serum globulins in excess of 3.5 per cent. Marked hyperproteinemia occurred particularly in persons with chronic complications, notably in those with rectal stricture. Of forty-two such individuals over 80 per cent showed hyperproteinemia with values up to 11.4 per cent. Repeated determinations, made over periods of almost 2 years, indicated that the elevated serum protein values tend to persist for indefinite periods at an approximately constant level. The significance of hyperproteinemia in lymphogranuloma is as yet unknown.

The Virus of Lymphogranuloma Venereum

The etiological agent of lymphogranuloma is a virus which is filterable through Berkefeld V or Chamberland L 3 candles. It is transmissible to monkeys, mice, guinea pigs, cats, dogs and to certain rodents such as the field vole, the spermophile and the striped ground squirrel. The virus can be observed microscopically in the form of cytoplasmic granules in the lesions of lymphogranuloma venereum of man, in the brains of infected monkeys, in the brains and lungs of infected mice, in experimental buboes in guinea pigs, and in the chorioallantoic membrane and yolk sac of the developing chick embryo. The dimensions of the virus, as shown by filtration through graded collodion membranes, are similar to those of the vaccinia virus, namely 0.125 to 0.175 micron.

The pathogenicity of strains of the virus for experimental animals is

low and little increase in virulence follows successive passage in them and in the chorioallantoic membrane of the chick.

The action of the virus can be inhibited by the use of sulfanilamide, sulfapyridine, sulfathiazole, [26, 27] and by other sulfonamide compounds.[27]

The Diagnosis of Lymphogranuloma Venereum

Owing to the lack of specificity of the histological lesions, accurate diagnosis of the disease is impossible by microscopic methods. None of the clinical manifestations are peculiar to lymphogranuloma, the most pathognomonic lesion being stricture with proctitis of which we have shown that 97 per cent of all cases are lymphogranulomatous (Table V). Detection of the virus in lesions requires highly trained personnel, considerable laboratory equipment, much time, and cannot always be carried out even in known cases of lymphogranuloma.

The cutaneous test discovered by Frei has proved to be highly specific and has been, until now, the sole means of accurate diagnosis. The test depends upon the fact that the skin of persons who have, or have had, lymphogranuloma is hypersensitive to the injection of the inactivated virus of the disease. Such hypersensitivity usually persists throughout the life of the individual. In one instance only, a laboratory infection in a worker, has the development and disappearance of this increased cutaneous reactivity been reported.[24]

The test is performed by the intradermal inoculation of an emulsion containing the inactivated virus. The inoculum is known as Frei antigen and the resulting reaction as the Frei reaction. Frei reactions are read at the end of 48 or 72 hours after the performance of the test. The positive reaction appears as an erythematous area, the central portion of which is more indurated and may take the form of a papule, papulovesicle or papulo-pustule according to the intensity of the reaction. The size of the erythematous area is of no diagnostic significance. Exact measurement, however, must be made of the dimensions of the papule when the test is read. The reading is positive when the diameter of the papule is not less than 6 or 7 millimeters, the figure depending upon whether the antigen has been prepared from human or chick, or mouse material. About three-quarters of all positive Frei reactions show a papule whose diameter ranges from 7 to 10 millimeters; the remainder give reactions larger than 10 millimeters. The original Frei antigen was prepared from bacteriologically sterile pus obtained from an unbroken

lymphogranulomatous bubo. The pus was diluted with approximately five times its volume of physiologic saline and the contained virus inactivated by heating at 60° C for two hours on one day and for one hour on the next. This material, now called human Frei antigen, is still used but is unsatisfactory for the following reasons: (1) it is difficult to be certain that the products of noxious agents other than the virus of lymphogranuloma are not present; (2) the supply of suitable pus is very limited; (3) the content of virus (and probably the virulence) varies considerably among different samples of pus; and (4) control material is unavailable.

It was in order to provide an unlimited supply of antigen, free from the disadvantages of human material, that mouse brain antigen was introduced by the author and Suskind[28] in 1934. This material is approximately an 8 per cent suspension, in physiologic saline, of mouse brain infected with a passage strain of the virus and inactivated in the same manner as in the preparation of human antigen. Mouse brain material has none of the drawbacks of human antigen and is a valuable diagnostic agent. It is not, however, a perfect product. In over three-quarters of the tests, mouse brain control gives non-specific reactions which are, nevertheless, distinguishable from positive reactions.

The ideal antigen would appear to be an inactivated emulsion of the granules of the virus. Such material has now been provided by Rake[15] following the growth of the virus in the yolk-sac of the developing chick embryo. The new antigen and control are practically water clear, and have been designated lygranum antigen and lygranum control respectively. Tests of lygranum antigen[29] indicate that it is at least the equal of mouse brain antigen in sensitivity and specificity.

Lygranum control is superior to mouse brain control in producing non-specific reactions in only 6 per cent of persons as compared with 78 per cent in the case of mouse material. Such non-specific reactions are readily distinguished from positive reactions.

It was stated above that the Frei cutaneous test was, until now, the sole means of accurate diagnosis of lymphogranuloma. Within the past 2 months Rake[30] and his colleagues have employed lygranum antigen in a complement-fixation test. The results obtained with the new test have been most striking. In well over 90 per cent of sera there was complete agreement between the results of the cutaneous and complement-fixation tests.[31] My own impression is that the new test is at least

the equal of the Frei test in specificity and sensitivity. It has already established a special place in those instances where the cutaneous reaction is doubtful or negative, in the presence of clinical manifestations which could be regarded as lymphogranulomatous. The new test may also permit of a more delicate appraisal of the progress of the disease than is possible now when reliance must be placed entirely upon symptomatic change. It may not replace the cutaneous test for routine work in the field, for reasons of convenience of performance, but I believe that it will come to be regarded as the final court of appeal in determining the lymphogranulomatous status of a clinical condition.

The Treatment of Lymphogranuloma Venereum

Prior to 1938 treatment was carried on in our clinic by a variety of methods. These included injection of Frei antigen or antimony compounds such as tartar emetic or fuadin; aspiration, excision or incision and drainage of buboes; performance of colostomy with or without resection of the rectum; dilatation of rectal strictures; topical application of balsam of Peru to areas of ulceration on the external genitalia or anorectal regions; x-ray to the groin or rectum; medicated enemata and general supportive measures. None of these procedures afforded ideal treatment. The most satisfactory results followed the use of Frei antigen, by the subcutaneous or intravenous routes, but only a small proportion of the cases dealt with in this manner responded well.

In 1938 Gjuric[32] reported good results in the treatment of twenty-three inguinal cases of lymphogranuloma by the use of a combination of fuadin and sulfanilamide. Shropshear[33] and Shaffer and Arnold,[34] in the same year, showed that the anorectal cases did unusually well following sulfanilamide therapy.

Between July 1938 and May 1940, thirty-one ambulatory cases showing various manifestations of lymphogranuloma were treated with sulfanilamide at the New York Hospital. The drug was given orally, usually commencing with 0.3 gm. to 0.6 gm. three times daily and increasing to 0.9 or 1.2 gm., three times daily. The exact dose depended upon the tolerance of the patient. Rest periods of 1 to 2 weeks were given on an average at 6 weekly intervals. In several cases, however, it was found necessary to discontinue the drug for a short time following 1 to 3 weeks' administration. Other patients, however, were able to take sulfanilamide continuously for 12 to 24 weeks without ill ef-

fects. When changes in the blood picture occurred, the duration of the rest period was extended. The average length of treatment, including rest periods, was, for the inguinal variety of the disease, 4 weeks, and for the anorectal, 29 weeks. No other treatment was employed except aspiration of fluctuant buboes. Of the inguinal cases 80 per cent were completely well within 3 to 6 weeks after beginning treatment and the remainder within 16 weeks. An average total dose of 52 grams of the drug were required. In the case of the anorectal variety, 39 per cent were completely healed within 9 to 79 weeks by the use of a total average dose of 172 grams of sulfanilamide. Improvement to a marked degree occurred in another 39 per cent and no less than 92 per cent of all the anorectal cases showed benefit from the treatment. The maximum total amount of the drug given to any healed patient was 330 grams during a period of 39 weeks. One individual, who did not respond at all to treatment, received 584 grams of sulfanilamide in 53 weeks. Untoward reactions, all minor in degree, occurred in 57 per cent of the individuals treated, and consisted of dizziness, headache, nausea and secondary anemia. There was no demonstrable relationship between the sulfanilamide content of the blood and the ultimate therapeutic effect of the drug.

Symptomatic relief coincided with the improvement in the proctoscopic appearance of the anorectal lesions, which began on an average 5 weeks after starting treatment. The passage of mucopurulent and bloody stools gradually diminished and finally ceased altogether; rectal, perianal or abdominal pain subsided; difficulty with bowel movements vanished and a feeling of well-being returned accompanied by a gain in weight and the disappearance of systemic manifestations including arthralgia and myalgia. Fibrous stricture of the rectum was not affected by sulfanilamide.

Frei tests were performed upon a number of persons in the group, before and after sulfanilamide therapy. No significant change in the degree of cutaneous reactivity resulted from the treatment.

Since May 1940 sulfathiazole has replaced sulfanilamide in the treatment of lymphogranuloma in our clinic. The dose employed has been 1.5 grams three times daily for 2 weeks, then 1.0 gram three times daily for the next 3 weeks. A rest period occupies the succeeding 3 weeks after which treatment is resumed, beginning with 1.5 grams three times daily as above. Inguinal cases of the disease do not usually require a

second five-week course of therapy. Results, to date, show a slightly more rapid response to sulfathiazole than was found with sulfanilamide. This may be due to the fact that the amount of sulfathiazole administered in a given time to any patient, has been almost double that previously employed in the case of sulfanilamide. No toxic manifestations have yet been observed with sulfathiazole.

The marked beneficial effect which has attended the use of sulfanilamide and sulfathiazole in the treatment of lymphogranuloma springs from the virostatic effect of these chemicals upon the etiological agent of the disease.

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